



(12) **United States Patent**
Hossainy et al.

(10) **Patent No.:** US 7,285,304 B1
(45) **Date of Patent:** Oct. 23, 2007

(54) FLUID TREATMENT OF A POLYMERIC COATING ON AN IMPLANTABLE MEDICAL DEVICE	5,028,597 A	7/1991	Kodama et al.
	5,059,211 A	10/1991	Stack et al.
	5,062,829 A	11/1991	Pryor et al.
	5,084,065 A	1/1992	Weldon et al.
	5,085,629 A	2/1992	Goldberg et al.
	5,100,429 A	3/1992	Sinofsky et al.
	5,104,410 A	4/1992	Chowdhary
	5,108,417 A	4/1992	Sawyer
	5,108,755 A	4/1992	Daniels et al.
	5,112,457 A	5/1992	Marchant
	5,123,917 A	6/1992	Lee
	5,156,623 A	10/1992	Hakamatsuka et al.
	5,163,951 A	11/1992	Pinchuk et al.
	5,163,952 A	11/1992	Froix
	5,163,958 A	11/1992	Pinchuk
	5,165,919 A	11/1992	Sasaki et al.
	5,167,614 A	12/1992	Tessmann et al.
	5,192,311 A	3/1993	King et al.
	5,197,977 A	3/1993	Hoffman, Jr. et al.
	5,234,456 A	8/1993	Silvestrini
	5,234,457 A	8/1993	Andersen
	5,236,447 A	8/1993	Kubo et al.
	5,272,012 A	12/1993	Opolski
	5,279,594 A	1/1994	Jackson

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,687,135 A	8/1972	Stroganov et al.
3,839,743 A	10/1974	Schwarcz
3,900,632 A	8/1975	Robinson
4,104,410 A	8/1978	Malecki
4,110,497 A	8/1978	Hoel
4,321,711 A	3/1982	Mano
4,329,383 A	5/1982	Joh
4,346,028 A	8/1982	Griffith
4,596,574 A	6/1986	Urist
4,599,085 A	7/1986	Riess et al.
4,612,009 A	9/1986	Drobnik et al.
4,633,873 A	1/1987	Dumican et al.
4,656,083 A	4/1987	Hoffman et al.
4,718,907 A	1/1988	Karwoski et al.
4,722,335 A	2/1988	Vilasi
4,723,549 A	2/1988	Wholey et al.
4,732,152 A	3/1988	Wallstén et al.
4,733,665 A	3/1988	Palmaz
4,739,762 A	4/1988	Palmaz
4,740,207 A	4/1988	Kreamer
4,743,252 A	5/1988	Martin, Jr. et al.
4,768,507 A	9/1988	Fischell et al.
4,776,337 A	10/1988	Palmaz
4,776,337 A	10/1988	Palmaz
4,800,882 A	1/1989	Gianturco
4,816,339 A	3/1989	Tu et al.
4,818,559 A	4/1989	Hama et al.
4,850,999 A	7/1989	Planck
4,877,030 A	10/1989	Beck et al.
4,878,906 A	11/1989	Lindemann et al.
4,879,135 A	11/1989	Greco et al.
4,882,168 A	11/1989	Casey et al.
4,886,062 A	12/1989	Wiktor
4,902,289 A	2/1990	Yannas
4,941,870 A	7/1990	Okada et al.
4,977,901 A	12/1990	Ofstead
4,994,298 A	2/1991	Yasuda
5,019,090 A	5/1991	Pinchuk

(Continued)

FOREIGN PATENT DOCUMENTS

DE 44 07 079 9/1994

(Continued)

OTHER PUBLICATIONS

Anonymous, *Rolling Therapeutic Agent Loading Device for Therapeutic Agent Delivery or Coated Stent* (Abstract 434009), Res. Disclos. pp. 974-975 (Jun. 2000).

(Continued)

Primary Examiner—Bret Chen*(74) Attorney, Agent, or Firm*—Squire, Sanders & Dempsey L.L.P.(57) **ABSTRACT**

A method of manufacturing an implantable medical device including applying a composition to an implantable medical device, the composition including a polymer, an active agent and a solvent; allowing the solvent to evaporate to form a dry coating, the dry coating comprising less than about 2% residual fluid content (w/w); applying a fluid to the dry coating, the fluid being substantially free from any polymer; and allowing the fluid to evaporate from the coating.

46 Claims, 5 Drawing Sheets

CORD120651

US 7,285,304 B1

Page 2

U.S. PATENT DOCUMENTS				
5,282,860 A	2/1994	Matsuno et al.	5,728,751 A	3/1998 Patnaik
5,289,831 A	3/1994	Bosley	5,733,326 A	3/1998 Tomonto et al.
5,290,271 A	3/1994	Jernberg	5,733,330 A	3/1998 Cox
5,292,516 A	3/1994	Viegas et al.	5,733,564 A	3/1998 Lehtinen
5,298,260 A	3/1994	Viegas et al.	5,733,925 A	3/1998 Kunz et al.
5,300,295 A	4/1994	Viegas et al.	5,735,897 A	4/1998 Buirge
5,306,286 A	4/1994	Stack et al.	5,741,881 A	4/1998 Patnaik
5,306,294 A	4/1994	Winston et al.	5,746,998 A	5/1998 Torchilin et al.
5,306,501 A	4/1994	Viegas et al.	5,756,457 A	5/1998 Wang et al.
5,328,471 A	7/1994	Slepian	5,756,476 A	5/1998 Epstein et al.
5,330,500 A	7/1994	Song	5,765,682 A	6/1998 Bley et al.
5,330,768 A	7/1994	Park et al.	5,766,204 A	6/1998 Porter et al.
5,342,348 A	8/1994	Kaplan	5,766,239 A	6/1998 Cox
5,342,395 A	8/1994	Jarrett et al.	5,766,710 A	6/1998 Turlund et al.
5,342,621 A	8/1994	Eury	5,769,883 A	6/1998 Buscemi et al.
5,356,433 A	10/1994	Rowland et al.	5,776,184 A	7/1998 Tuch
5,380,299 A	1/1995	Fearnott et al.	5,780,807 A	7/1998 Saunders
5,383,925 A	1/1995	Schmitt	5,788,979 A	8/1998 Alt et al.
5,385,580 A	1/1995	Schmitt	5,800,392 A	9/1998 Racchini
5,389,106 A	2/1995	Tower	5,800,516 A	9/1998 Fine et al.
5,399,666 A	3/1995	Ford	5,811,447 A	9/1998 Kunz et al.
5,417,981 A	5/1995	Endo et al.	5,820,917 A	10/1998 Tuch
5,423,885 A	6/1995	Williams	5,824,048 A	10/1998 Tuch
5,441,515 A	8/1995	Khosravi et al.	5,824,049 A	10/1998 Ragheb et al.
5,443,458 A	8/1995	Eury et al.	5,830,178 A	11/1998 Jones et al.
5,443,500 A	8/1995	Sigwart	5,830,461 A	11/1998 Billiar
5,447,724 A	9/1995	Helmus et al.	5,830,879 A	11/1998 Isner
5,455,040 A	10/1995	Marchant	5,833,651 A	11/1998 Donovan et al.
5,462,990 A	10/1995	Hubbell et al.	5,834,582 A	11/1998 Sinclair et al.
5,464,650 A	11/1995	Berg et al.	5,836,962 A	11/1998 Gianotti
5,502,158 A	3/1996	Sinclair et al.	5,837,008 A	11/1998 Berg et al.
5,514,379 A	5/1996	Weissleder et al.	5,837,313 A	11/1998 Ding et al.
5,527,337 A	6/1996	Stack et al.	5,837,835 A	11/1998 Gryaznov et al.
5,545,408 A	8/1996	Trigg et al.	5,840,083 A	11/1998 Braach-Maksvytis
5,554,120 A	9/1996	Chen et al.	5,851,508 A	12/1998 Greff et al.
5,556,413 A	9/1996	Lam	5,853,408 A	12/1998 Muni
5,569,463 A	10/1996	Helmus et al.	5,854,207 A	12/1998 Lee et al.
5,578,046 A	11/1996	Liu et al.	5,855,612 A	1/1999 Oththuki et al.
5,578,073 A	11/1996	Haimovich et al.	5,855,618 A	1/1999 Patnaik et al.
5,591,199 A	1/1997	Porter et al.	5,858,746 A	1/1999 Hubbell et al.
5,591,607 A	1/1997	Gryaznov et al.	5,865,814 A	2/1999 Tuch
5,593,403 A	1/1997	Buscemi	5,868,781 A	2/1999 Killion
5,593,434 A	1/1997	Williams	5,869,127 A	2/1999 Zhong
5,599,301 A	2/1997	Jacobs et al.	5,873,904 A	2/1999 Ragheb et al.
5,599,922 A	2/1997	Gryaznov et al.	5,874,101 A	2/1999 Zhong et al.
5,605,696 A	2/1997	Eury et al.	5,874,109 A	2/1999 Ducheyne et al.
5,607,442 A	3/1997	Fischell et al.	5,874,165 A	2/1999 Drumheller
5,607,467 A	3/1997	Froix	5,876,433 A	3/1999 Lunn
5,609,629 A	3/1997	Fearnott et al.	5,876,743 A	3/1999 Ibsen et al.
5,618,299 A	4/1997	Khosravi et al.	5,877,224 A	3/1999 Brocchini et al.
5,624,411 A	4/1997	Tuch	5,877,263 A	3/1999 Patnaik et al.
5,628,730 A	5/1997	Shapland et al.	5,879,713 A	3/1999 Roth et al.
5,629,077 A	5/1997	Turnlund et al.	5,888,533 A	3/1999 Dunn
5,631,135 A	5/1997	Gryaznov et al.	5,891,192 A	4/1999 Murayama et al.
5,632,771 A	5/1997	Boatman et al.	5,897,955 A	4/1999 Drumheller
5,632,840 A	5/1997	Campbell	5,906,759 A	5/1999 Richter
5,637,113 A	6/1997	Tartaglia et al.	5,914,182 A	6/1999 Drumheller
5,649,977 A	7/1997	Campbell	5,916,870 A	6/1999 Lee et al.
5,658,995 A	8/1997	Kohn et al.	5,922,005 A	7/1999 Richter et al.
5,667,767 A	9/1997	Greff et al.	5,925,720 A	7/1999 Kataoka et al.
5,667,796 A	9/1997	Otten	5,942,209 A	8/1999 Leavitt et al.
5,670,558 A	9/1997	Onishi et al.	5,948,428 A	9/1999 Lee et al.
5,679,400 A	10/1997	Tuch	5,954,744 A	9/1999 Phan et al.
5,693,085 A	12/1997	Buirge et al.	5,955,509 A	9/1999 Webber et al.
5,700,286 A	12/1997	Tartaglia et al.	5,957,975 A	9/1999 Lafont et al.
5,702,754 A	12/1997	Zhong	5,965,720 A	10/1999 Gryaznov et al.
5,707,385 A	1/1998	Williams	5,971,954 A	10/1999 Conway et al.
5,711,763 A	1/1998	Nonami et al.	5,976,182 A	11/1999 Cox
5,716,981 A	2/1998	Hunter et al.	5,980,564 A	11/1999 Stinson
5,725,549 A	3/1998	Lam	5,980,928 A	11/1999 Terry
5,726,297 A	3/1998	Gryaznov et al.	5,981,568 A	11/1999 Kunz et al.
			5,986,169 A	11/1999 Gjunter

CORD120652

US 7,285,304 B1

Page 3

5,997,468 A	12/1999	Wolff et al.	6,293,966 B1	9/2001	Frantzen
5,997,517 A	12/1999	Whitbourne	6,299,604 B1	10/2001	Ragheb et al.
6,010,445 A	1/2000	Armini et al.	6,303,901 B1	10/2001	Perry et al.
6,010,530 A	1/2000	Goiocochea	6,306,176 B1	10/2001	Whitbourne
6,015,541 A	1/2000	Greff et al.	6,312,459 B1	11/2001	Huang et al.
6,033,582 A	3/2000	Lee et al.	6,327,772 B1	12/2001	Zadno-Azizi et al.
6,042,875 A	3/2000	Ding et al.	6,331,313 B1	12/2001	Wong et al.
6,048,964 A	4/2000	Lee et al.	6,335,029 B1	1/2002	Kamath et al.
6,051,576 A	4/2000	Ashton et al.	6,346,110 B2	2/2002	Wu
6,051,648 A	4/2000	Rhee et al.	6,358,556 B1 *	3/2002	Ding et al. 427/2.24
6,056,993 A	5/2000	Leidner et al.	6,375,826 B1	4/2002	Wang et al.
6,060,451 A	5/2000	DiMaio et al.	6,379,381 B1	4/2002	Hossainy et al.
6,060,518 A	5/2000	Kabanov et al.	6,387,121 B1	5/2002	Alt
6,066,156 A	5/2000	Yan	6,387,124 B1	5/2002	Buscemi et al.
6,071,266 A	6/2000	Kelley	6,388,043 B1	5/2002	Langer et al.
6,074,659 A	6/2000	Kunz et al.	6,395,326 B1	5/2002	Castro et al.
6,080,177 A	6/2000	Igaki et al.	6,409,761 B1	6/2002	Jang
6,080,488 A	6/2000	Hostettler et al.	6,419,692 B1	7/2002	Yang et al.
6,083,258 A	7/2000	Yadav	6,423,092 B2	7/2002	Datta et al.
6,093,463 A	7/2000	Thakrar	6,451,373 B1	9/2002	Hossainy et al.
6,096,070 A	8/2000	Ragheb et al.	6,461,632 B1	10/2002	Gogolewski
6,096,525 A	8/2000	Patnaik	6,464,720 B2	10/2002	Boatman et al.
6,099,562 A *	8/2000	Ding et al. 623/1.46	6,479,565 B1	11/2002	Stanley
6,103,230 A	8/2000	Billiar et al.	6,485,512 B1	11/2002	Cheng
6,107,416 A	8/2000	Patnaik et al.	6,492,615 B1	12/2002	Flanagan
6,110,188 A	8/2000	Narciso, Jr.	6,494,862 B1	12/2002	Ray et al.
6,110,483 A	8/2000	Whitbourne et al.	6,494,908 B1	12/2002	Huxel et al.
6,113,629 A	9/2000	Ken	6,495,156 B2	12/2002	Wenz et al.
6,117,979 A	9/2000	Hendriks et al.	6,503,556 B2	1/2003	Harish et al.
6,120,536 A	9/2000	Ding et al.	6,503,954 B1	1/2003	Bhat et al.
6,120,904 A	9/2000	Hostettler et al.	6,506,437 B1	1/2003	Harish et al.
6,121,027 A	9/2000	Clapper et al.	6,511,748 B1	1/2003	Barrows
6,125,523 A	10/2000	Brown et al.	6,517,888 B1	2/2003	Weber
6,127,173 A	10/2000	Eckstein et al.	6,527,801 B1	3/2003	Dutta
6,129,761 A	10/2000	Hubbell	6,527,863 B1	3/2003	Pacetti et al.
6,129,928 A	10/2000	Sarangapani et al.	6,534,112 B1 *	3/2003	Bouchier et al. 427/2.24
6,150,630 A	11/2000	Perry et al.	6,537,589 B1	3/2003	Chae et al.
6,153,252 A	11/2000	Hossainy et al.	6,539,607 B1	4/2003	Fehring et al.
6,159,951 A	12/2000	Karpeisky et al.	6,540,776 B2	4/2003	Sanders Millare et al.
6,160,084 A	12/2000	Langer et al.	6,540,777 B2	4/2003	Stenzel
6,165,212 A	12/2000	Dereume et al.	6,544,223 B1	4/2003	Kokish
6,166,130 A	12/2000	Rhee et al.	6,544,543 B1	4/2003	Mandrusov et al.
6,169,170 B1	1/2001	Gryaznov et al.	6,544,582 B1	4/2003	Yoe
6,171,609 B1	1/2001	Kunz	6,554,854 B1	4/2003	Flanagan
6,174,330 B1	1/2001	Stinson	6,555,157 B1	4/2003	Hossainy
6,177,523 B1	1/2001	Reich et al.	6,558,733 B1	5/2003	Hossainy et al.
6,183,505 B1	2/2001	Mohn, Jr. et al.	6,565,599 B1	5/2003	Hong et al.
6,187,045 B1	2/2001	Fehring et al.	6,565,659 B1	5/2003	Pacetti et al.
6,203,551 B1	3/2001	Wu	6,569,191 B1	5/2003	Hogan
6,210,715 B1	4/2001	Starling et al.	6,569,193 B1	5/2003	Cox et al.
6,214,901 B1	4/2001	Chudzik et al.	6,572,644 B1	6/2003	Moein
6,224,626 B1	5/2001	Steinke	6,572,672 B2	6/2003	Yadav et al.
6,228,845 B1	5/2001	Donovan et al.	6,574,851 B1	6/2003	Mirizzi
6,231,600 B1	5/2001	Zhong	6,585,755 B2	7/2003	Jackson et al.
6,240,616 B1	6/2001	Yan	6,585,765 B1	7/2003	Hossainy et al.
6,245,076 B1	6/2001	Yan	6,585,926 B1	7/2003	Mirzaee
6,245,103 B1	6/2001	Stinson	6,592,614 B2	7/2003	Lenker et al.
6,245,753 B1	6/2001	Byun et al.	6,592,617 B2	7/2003	Thompson
6,248,344 B1	6/2001	Ylanc et al.	6,605,154 B1	8/2003	Villarcal
6,251,135 B1	6/2001	Stinson et al.	6,613,072 B2	9/2003	Lau et al.
6,251,136 B1	6/2001	Guruwaiya et al.	6,626,939 B1	9/2003	Burnside et al.
6,251,142 B1	6/2001	Bernacca et al.	6,635,269 B1	10/2003	Jennissen
6,254,632 B1	7/2001	Wu et al.	6,645,243 B2	11/2003	Vallana et al.
6,258,121 B1	7/2001	Yang et al.	6,656,162 B2	12/2003	Santini, Jr. et al.
6,273,913 B1	8/2001	Wright et al.	6,664,335 B2	12/2003	Krishnan
6,281,262 B1	8/2001	Shikinami	6,666,214 B2	12/2003	Canham
6,283,947 B1	9/2001	Mirzaee	6,667,049 B2	12/2003	Janas et al.
6,283,949 B1	9/2001	Roorda	6,669,723 B2	12/2003	Killion et al.
6,284,305 B1	9/2001	Ding et al.	6,669,980 B2 *	12/2003	Hansen 427/2.24
6,284,333 B1	9/2001	Wang et al.	6,676,697 B1	1/2004	Richter
6,287,332 B1	9/2001	Bolz et al.	6,679,980 B1	1/2004	Andreacchi
6,287,628 B1	9/2001	Hossainy et al.	6,689,375 B1	2/2004	Wahlig et al.
6,290,721 B1	9/2001	Heath	6,695,920 B1	2/2004	Pacetti et al.

CORD120653

US 7,285,304 B1

Page 4

6,706,273	B1	3/2004	Roessler	EP	0 910 584	4/1999
6,709,379	B1	3/2004	Brandau et al.	EP	0 923 953	6/1999
6,719,934	B2	4/2004	Stinson	EP	0 953 320	11/1999
6,719,989	B1	4/2004	Matsushima et al.	EP	0 970 711	1/2000
6,720,402	B2	4/2004	Langer et al.	EP	0 982 041	3/2000
6,746,773	B2	6/2004	Llanos et al.	EP	1 273 314	1/2003
6,752,826	B2	6/2004	Holloway et al.	GB	2 247 696	3/1992
6,753,007	B2	6/2004	Haggard et al.	JP	2001-190687	7/2001
6,764,505	B1	7/2004	Hossainy et al.	WO	WO89/03232	4/1989
6,818,063	B1	11/2004	Kerrigan	WO	WO90/01969	3/1990
6,846,323	B2	1/2005	Yip et al.	WO	WO90/04982	5/1990
2001/0018469	A1	8/2001	Chen et al.	WO	WO90/06094	6/1990
2001/0037145	A1	11/2001	Guruwaiya et al.	WO	WO91/12846	9/1991
2001/0044652	A1	11/2001	Moore	WO	WO91/17744	11/1991
2002/0002399	A1	1/2002	Huxel et al.	WO	WO91/17789	11/1991
2002/0004060	A1	1/2002	Heublein et al.	WO	WO92/10218	6/1992
2002/0004101	A1	1/2002	Ding et al.	WO	WO93/06792	4/1993
2002/0062148	A1	5/2002	Hart	WO	WO94/21196	9/1994
2002/0065553	A1	5/2002	Weber	WO	WO95/10989	4/1995
2002/0077693	A1	6/2002	Barclay et al.	WO	WO95/29647	11/1995
2002/0091433	A1	7/2002	Ding et al.	WO	WO96/40174	12/1996
2002/0111590	A1	8/2002	Davila et al.	WO	WO97/10011	3/1997
2002/0116050	A1	8/2002	Kocur	WO	WO97/45105	12/1997
2002/0138133	A1	9/2002	Lenz et al.	WO	WO97/46590	12/1997
2002/0155212	A1	10/2002	Hossainy	WO	WO98/04415	2/1998
2002/0161114	A1	10/2002	Gunatillake et al.	WO	WO98/17331	4/1998
2003/0033001	A1	2/2003	Igaki	WO	WO98/36784	8/1998
2003/0065377	A1	4/2003	Davila et al.	WO	WO99/01118	1/1999
2003/0093107	A1	5/2003	Parsonage et al.	WO	WO99/03515	1/1999
2003/0099712	A1	5/2003	Jayaraman	WO	WO99/16386	4/1999
2003/0100865	A1	5/2003	Santini, Jr. et al.	WO	WO99/38546	8/1999
2003/0105518	A1	6/2003	Dutta	WO	WO99/42147	8/1999
2003/0105530	A1	6/2003	Pirhonen	WO	WO99/63981	12/1999
2003/0171053	A1	9/2003	Sanders	WO	WO 00/02599	1/2000
2003/0187495	A1	10/2003	Cully et al.	WO	WO 00/12147	3/2000
2003/0208259	A1	11/2003	Penhasi	WO	WO 00/18446	4/2000
2003/0209835	A1	11/2003	Chun et al.	WO	WO 00/32238	6/2000
2003/0226833	A1	12/2003	Shapovalov et al.	WO	WO 00/64506	11/2000
2003/0236565	A1	12/2003	Fifer	WO	WO 01/01890	1/2001
2004/0093077	A1	5/2004	White et al.	WO	WO 01/15751	3/2001
2004/0098095	A1	5/2004	Burnside et al.	WO	WO 01/17577	3/2001
2004/0111149	A1	6/2004	Stinson	WO	WO 01/45763	6/2001
2004/0127970	A1	7/2004	Weber	WO	WO 01/49338	7/2001
2004/0143317	A1	7/2004	Stinson et al.	WO	WO 01/74414	10/2001
2004/0167610	A1	8/2004	Fleming, III	WO	WO 02/003890	1/2002
2004/0220665	A1 *	11/2004	Hossainy et al.	WO	WO 02/026162	4/2002
2004/0258728	A1 *	12/2004	Nchekwube et al.	WO	WO 02/34311	5/2002
				WO	WO 02/056790	7/2002
				WO	WO 03/000308	1/2003
DE	197 31 021	1/1999		WO	WO 03/022323	* 3/2003
DE	198 56 983	12/1999		WO	WO 03/028780	4/2003
EP	0 108 171	5/1984		WO	WO 03/037223	5/2003
EP	0 144 534	6/1985		WO	WO 03/039612	5/2003
EP	0 301 856	2/1989		WO	WO 2004/023985	3/2004
EP	0 364 787	4/1990				
EP	0 397 500	11/1990				
EP	0 464 755	1/1992				
EP	0 493 788	7/1992				
EP	0 514 406	11/1992				
EP	0 554 082	8/1993				
EP	0 578 998	1/1994				
EP	0 604 022	6/1994				
EP	0 621 017	10/1994				
EP	0 623 354	11/1994				
EP	0 665 023	8/1995				
EP	0 701 802	3/1996				
EP	0 709 068	5/1996				
EP	0 716 836	6/1996				
EP	0 809 999	12/1997				
EP	0 832 655	4/1998				
EP	0 850 651	7/1998				
EP	0 879 595	11/1998				

FOREIGN PATENT DOCUMENTS

DE	197 31 021	1/1999
DE	198 56 983	12/1999
EP	0 108 171	5/1984
EP	0 144 534	6/1985
EP	0 301 856	2/1989
EP	0 364 787	4/1990
EP	0 397 500	11/1990
EP	0 464 755	1/1992
EP	0 493 788	7/1992
EP	0 514 406	11/1992
EP	0 554 082	8/1993
EP	0 578 998	1/1994
EP	0 604 022	6/1994
EP	0 621 017	10/1994
EP	0 623 354	11/1994
EP	0 665 023	8/1995
EP	0 701 802	3/1996
EP	0 709 068	5/1996
EP	0 716 836	6/1996
EP	0 809 999	12/1997
EP	0 832 655	4/1998
EP	0 850 651	7/1998
EP	0 879 595	11/1998

OTHER PUBLICATIONS

- Aoyagi et al., *Preparation of cross-linked aliphatic polyester and application to thermo-responsive material*, Journal of Controlled Release 32:87-96 (1994).
- Baird et al., *Dielectric behaviour and morphology of polyvinylidene fluoride*, Journal of Material Science 10:1248-1251 (1975).
- Barath et al., *Low Dose of Antitumor Agents Prevents Smooth Muscle Cell Proliferation After Endothelial Injury*, JACC 13(2): 252A (Abstract) (Feb. 1989).
- Barbucci et al., *Coating of commercially available materials with a new heparinizable material*, J. Biomed. Mater. Res. 25:1259-1274 (Oct. 1991).
- Black et al., *Glass Transitions of Some Block Copolymers*, Journal of Applied Polymer Science 18:2307-2310 (1974).
- Bliznyuk et al., *Surface Glass Transition Temperature of Amorphous Polystyrene Measured By SFM*, p. 1-5, no date.

CORD120654

US 7,285,304 B1

Page 5

- Buchholz et al., *Cooling rate dependence of the glass transition temperature of polymer melts: Molecular dynamics study*, Journal of Chemical Physics 117(15):7364-7372 (Oct. 15, 2002).
- Chung et al., *Inner core segment design for drug delivery control of thermo-responsive polymeric micelles*, Journal of Controlled Release 65:93-103 (2000).
- Dev et al., *Kinetics of Drug Delivery to the Arterial Wall Via Polyurethane-Coated Removable Nitinol Stent: Comparative Study of Two Drugs, Catheterization and Cardiovascular Diagnosis* 34:272-278 (1995).
- Dichek et al., *Seeding of Intravascular Stents with Genetically Engineered Endothelial Cells*, Circ. 80(5):1347-1353 (Nov. 1989).
- Ding et al., *Novel Synthesis of Poly(p-phenylene sulfide) from Cyclic Disulfide Oligomers*, Macromolecules 29:4811-4812 (1996).
- Eigler et al., *Local Arterial Wall Drug Delivery from a Polymer Coated Removable Metallic Stent: Kinetics, Distribution, and Bioactivity of Forskolin*, JACC, 4A (701-1), Abstract (Feb. 1994), no page numbers.
- Fernandez-Martin et al., *Glass Transition Temperature and Heat Capacity of Heterotacticlike PMMA*, Journal of Polymer Science: Polymer Physics Edition 19:1353-1363 (1981).
- Forrest et al., *Effect of Free Surfaces on the Glass Transition Temperature of Thin Polymer Films*, Physical Review Letters 77(10):2002-2005 (Sep. 2, 1996).
- Fryer et al., *Dependence of the Glass Transition Temperature of Polymer Films on Interfacial Energy and Thickness*, Macromolecules 34(16):5627-5634 (2001).
- Fujii et al., *Investigation of the Stereoregularity of Poly(vinyl Alcohol)*, Journal of Polymer Science: Part A:2:2327-2347 (1964).
- Gee et al., *The effect of ionizing radiation on the thermal properties of linear high polymers: Part 2. Nylon-6*, pp. 192-197 (1970).
- Grohens et al., *Tacticity and surface chemistry effects on the glass transition temperature of thin supported PMMA films*, Mat. Res. Soc. Symp. 629:FF1.7.1-FF1.7.7 (2000).
- Helmus, *Overview of Biomedical Materials*, MRS Bulletin, pp. 33-38 (Sep. 1991).
- Herdeg et al., *Antiproliferative Stent Coatings: Taxol and Related Compounds*, Semin. Intervent. Cardiol. 3:197-199 (1998).
- Inoue et al., *An AB block copolymer of oligo(methyl methacrylate) and poly(acrylic acid) for micellar delivery of hydrophobic drugs*, Journal of Controlled Release 51:221-229 (1998).
- Kataoka et al., *Block copolymer micelles as vehicles for drug delivery*, Journal of Controlled Release 24:119-132 (1993).
- Levy et al., *Strategies For Treating Arterial Restenosis Using Polymeric Controlled Release Implants*, Biotechnol. Bioact. Polym. [Proc. Am. Chem. Soc. Symp.], pp. 259-268 (1994).
- Löfgren et al., *Synthesis and Characterization of Biodegradable Homopolymers and Block Copolymers Based on 1,5-Dioxepan-2-one*, Macromolecules 27:5556-5562 (1994).
- Liu et al., *Drug release characteristics of unimolecular polymeric micelles*, Journal of Controlled Release 68:167-174 (2000).
- Lotz, *Phase Transitions and Structure of Crystalline Polymers*, pp. 1-27, no date.
- Marconi et al., *Covalent bonding of heparin to a vinyl copolymer for biomedical applications*, Biomaterials 18(12):885-890 (1997).
- Matsumaru et al., *Embolic Materials For Endovascular Treatment of Cerebral Lesions*, J. Biomater. Sci. Polymer Edn 8(7):555-569 (1997).
- Micoulaut et al., *Glass Transition temperature variation, cross-linking and structure in network glasses: A stochastic approach*, Europhysics Letters 47(5):568-574 (Sep. 1, 1999).
- Miyazaki et al., *Antitumor Effect of Implanted Ethylene-Vinyl Alcohol Copolymer Matrices Containing Anticancer Agents on Ehrlich Ascites Carcinoma and P388 Leukemia in Mice*, Chem. Pharm. Bull. 33(6) 2490-2498 (1985).
- Miyazawa et al., *Effects of Pemirolast and Tranilast on Intimal Thickening After Arterial Injury in the Rat*, J. Cardiovasc. Pharmacol., pp. 157-162 (1997).
- Nordrehaug et al., *A novel biocompatible coating applied to coronary stents*, European Heart Journal 14, p. 321 (P1694), Abstr. Suppl. (1993).
- Ohsawa et al., *Preventive Effects of an Antiallergic Drug, Pemirolast Potassium, on Restenosis After Percutaneous Transluminal Coronary Angioplasty*, American Heart Journal 136(6):1081-1087 (Dec. 1998).
- Ozaki et al., *New Stent Technologies*, Progress in Cardiovascular Diseases, vol. XXXIX(2):129-140 (Sep./Oct. 1996).
- Paravicini et al., *Crystallization of Poly(Ethylene Terephthalate) (PET) from the Oriented Mesomorphic Form*, pp. 875-885 (1994).
- Pechar et al., *Poly(ethylene glycol) Multiblock Copolymers as a Carrier of Anti-Cancer Drug Doxorubicin*, Biocjugate Chemistry 11(2):131-139 (Mar./Apr. 2000).
- Peng et al., *Role of polymers in improving the results of stenting in coronary arteries*, Biomaterials 17:685-694 (1996).
- Rogers et al., *Glass Formation in Polymers. I. The Glass Transitions of the Poly-(n-Alkyl Methacrylates)*, 61:985-990 (Jul. 1957).
- Scott et al., *Ethylene-Vinyl Acetate Semi-Batch Emulsion Copolymerization: Use of Factorial Experiments for Process Optimization*, pp. 539-555 (1993).
- Shigeno, *Prevention of Cerebrovascular Spasm By Bosentan, Novel Endothelin Receptor*, Chemical Abstract 125:212307 (1996).
- Sichima, *Characterization of Polymers by TMA*, Perkin Elmer Polymers technical note (9 pages), no date.
- Sun et al., *Novel Copolymers Containing Naphthalene Structure. I. Form Bis(hydroxylalkyl)naphthalate and Bis[f4-(2-hydroxyethoxy)aryl] Compounds*, Journal of Polymer Science: Part A: Polymer Chemistry 34:1783-1792 (1996).
- Taylor et al., *Applied approach to film formation: The glass transition temperature evolution of plasticized latex films* (22 pages), no date.
- Tsige et al., *Stimulation of the glass transition temperature in poly(methyl methacrylate)*, Physical Review E 65:021805-1-021805-8 (2002).
- van Beusekom et al., *Coronary stent coatings*, Coronary Artery Disease 5(7):590-596 (Jul. 1994).
- Wilensky et al., *Methods and Devices for Local Drug Delivery in Coronary and Peripheral Arteries*, Trends Cardiovasc. Med. 3(5):163-170 (1993).
- Yokoyama et al., *Characterization of physical entrapment and chemical conjugation of adriamycin in polymeric micelles and their design for in vivo delivery to a solid tumor*, Journal of Controlled Release 50:79-92 (1998).
- U.S. Appl. No. 10/317,435, filed Dec. 11, 2002, Hossainy et al.
- Anonymous, *Bioabsorbable stent mounted on a catheter having optical coherence tomography capabilities*, Research Disclosure, Sep. 2004, pp. 1159-1162.
- Ansari, *Tubal Reanastomosis Using Absorbable Stent*, International Journal of Fertility, vol. 23, No. 4, pp. 242-243 (1978).
- Ansari, *End-to-end tubal anastomosis using an absorbable stent*, Fertility and Sterility, vol. 32(2), pp. 197-201 (Aug. 1979).
- Bull, *Parylene Coating for Medical Applications*, Medical Product Manufacturing News 1 pg. (Mar. 1993).
- Casper et al., *Fiber-Reinforced Absorbable Composite for Orthopedic Surgery*, Polymeric Materials Science and Engineering, 53: pp. 497-501 (1985).
- Detweiler et al., *Sutureless Anastomosis of the Small Intestine and the Colon in Pigs Using an Absorbable Intraluminal Stent and Fibrin Glue*, Journal of Investigative Surgery, vol. 8(2), pp. 129-140 (Mar. 1995).
- Detcwiler et al., *Sutureless Cholecystojjunostomy in Pigs Using an Absorbable Intraluminal Stent and Fibrin Glue*, Journal of Investigative Surgery, vol. 9(1), pp. 13-26 (Jan./Feb. 1996).
- Detweiler et al., *Sliding, Absorbable, Reinforced Ring and an Axially Driven Stent Placement Device for Sutureless Fibrin Glue Gastrointestinal Anastomosis*, Journal of Investigative Surgery, vol. 9(6), pp. 495-504 (Nov./Dec. 1996).
- Detweiler et al., *Gastrointestinal Sutureless Anastomosis Using Fibrin Glue: Reinforcement of the Sliding Absorbable Intraluminal Nontoxic Stent and Development of a Stent Placement Device*, Journal of Investigative Surgery, vol. 9(2), pp. 111-130 (Mar./Apr. 1996).
- Devanathan et al., *Polymeric Conformal Coatings for Implantable Electronic Devices*, IEEE Transactions on Biomedical Engineering, vol. BME-27(11), pp. 671-675 (1980).

CORD120655

US 7,285,304 B1

Page 6

- Elbert et al., *Conjugate Addition Reactions Combined with Free-Radical Cross-Linking for the Design of Materials for Tissue Engineering*, Biomacromolecules 2, pp. 430-441 (2001).
- Feng-Chun et al., *Assessment of Tissue Blood Flow Following Small Artery Welding with an Intraluminal Dissolvable Stent*, Microsurgery, vol. 19(3), 148-152 (1999).
- Hahn et al., *Glow Discharge Polymers as Coatings for Implanted Devices*, ISA, pp. 109-111 (1981).
- Hahn et al., *Biocompatibility of Glow-Discharge-Polymerized Films and Vacuum-Deposited Parylene*, J. Applied Polymer Sci, 38, pp. 55-64 (1984).
- Kelley et al., *Totally Resorbable High-Strength Composite Material*, Advances in Biomedical Polymers, 35, pp. 75-85 (1987).
- Kubies et al., *Microdomain Structure In polyactide-block-poly(ethylene oxide) copolymers films*, Biomaterials 21, pp. 529-536 (2000).
- Kutryk et al., *Coronary Stenting: Current Perspectives*, a companion to the Handbook of Coronary Stents 16 pgs. (1999).
- Mauduit et al., *Hydrolytic degradation of films prepared from blends of high and low molecular weight poly(DL-lactic acid)s*, J. Biomed. Mater. Res. v. 30, pp. 201-207 (1996).
- Martin et al., *Enhancing the biological activity of immobilized osteopontin using a type-I collagen affinity coating*, J. Biomed. Mater Res 70A, pp. 10-19 (2004).
- Middleton et al., *Synthetic biodegradable polymers as orthopedic devices*, Biomaterials, vol. 21, pp. 2335-2346 (2000).
- Muller et al., *Advances in Coronary Angioplasty: Endovascular Stents*, Coron. Arter. Dis., 1(4), pp. 438-448 (Jul/Aug. 1990).
- Nichols et al., *Electrical Insulation of Implantable Devices by Composite Polymer Coatings*, ISA Transactions, 26(4), pp. 15-18 (1987).
- Peuster et al., *A novel approach to temporary stenting: degradable cardiovascular stents produced from corrodible metal-results 6-18 months after implantation into New Zealand white rabbits*, Heart 86, pp. 563-569 (2001).
- Pietrzak et al., *Bioresorbable implants—practical considerations*, Bone v. 19, No. 1, Supplement Jul. 1996: 109S-119S.
- Pietrzak et al., *Biabsorbable Fixation Devices: Status for the Craniomaxillofacial Surgeon*, J. Craniofacial Surg. 2, pp. 92-96 (1997).
- von Recum et al., *Degradation of polydispersed poly(L-lactic acid) to modulate lactic acid release*, Biomaterials 16, pp. 441-445 (1995).
- Redman, *Clinical Experience with Vasovasostomy Utilizing Absorbable Intravasal Stent*, Urology, vol. 20(1), pp. 59-61 (Jul. 1982).
- Rust et al., *The Effect of Absorbable Stenting on Postoperative Stenosis of the Surgically Enlarged Maxillary Sinus Ostia in a Rabbit Animal Model*, Archives of Otolaryngology, vol. 122(12) pp. 1395-1397 (Dec. 1996).
- Schatz, *A View of Vascular Stents*, Circulation, 79(2), pp. 445-457 (Feb. 1989).
- Schmidt et al., *Long-Term Implants of Parylene-C Coated Microelectrodes*, Med & Biol Eng & Comp, 26(1), pp. 96-101 (Jan. 1988).
- Spagnuolo et al., *Gas I is induced by VE-cadherin and vascular endothelial growth factor and inhibits endothelial cell apoptosis*, Blood 103, pp. 3005-3012 (2004).
- Tamai et al., *Initial and 6-Month Results of Biodegradable Poly-L-Lactic Acid Coronary Stents in Humans*, Circulation , pp. 399-404 (2000).
- Tsui et al., *Biodegradable Polymeric Stents*, Current Interventional Cardiology Reports 3, pp. 10-17 (2001).
- Völkel et al., *Targeting of immunoliposomes to endothelial cells using a single -chain Fv fragment directed against human endoglin (CD105)*, Biochimica et Biophysica Acta 1663, pp. 158-166 (2004).
- Yau et al. Modern Size-Exclusion Liquid Chromatography, Wiley-Interscience Publication, (1979).

* cited by examiner

CORD120656

A1329

U.S. Patent

Oct. 23, 2007

Sheet 1 of 5

US 7,285,304 B1

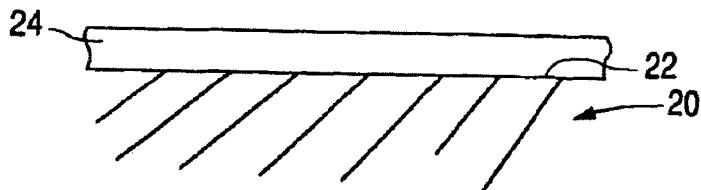


FIG. 1A

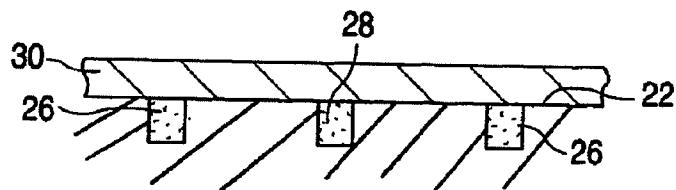


FIG. 1B

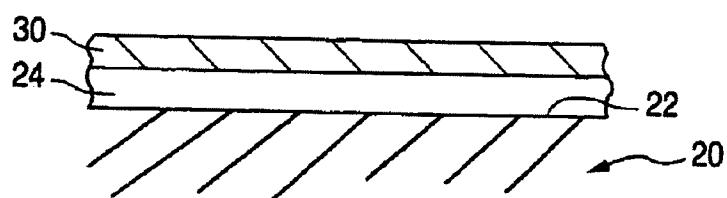


FIG. 1C

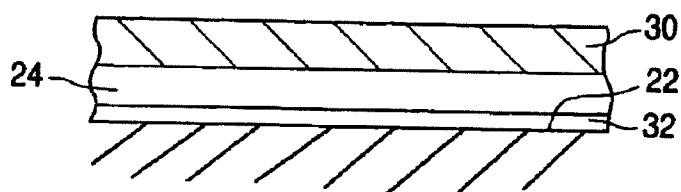


FIG. 1D

CORD120657

A1330

U.S. Patent

Oct. 23, 2007

Sheet 2 of 5

US 7,285,304 B1

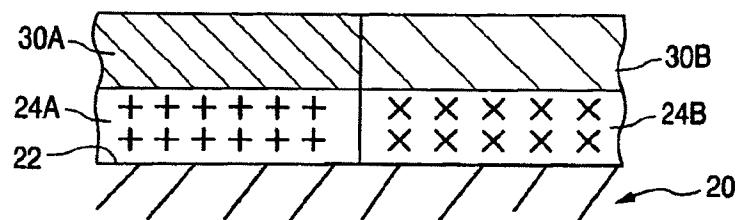


FIG. 1E

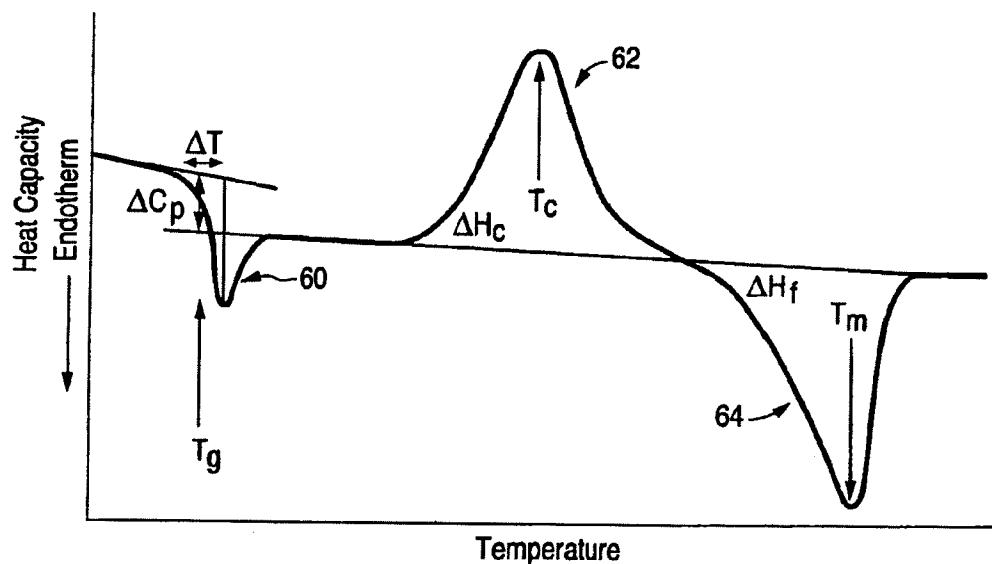


FIG. 2

CORD120658

A1331

U.S. Patent

Oct. 23, 2007

Sheet 3 of 5

US 7,285,304 B1

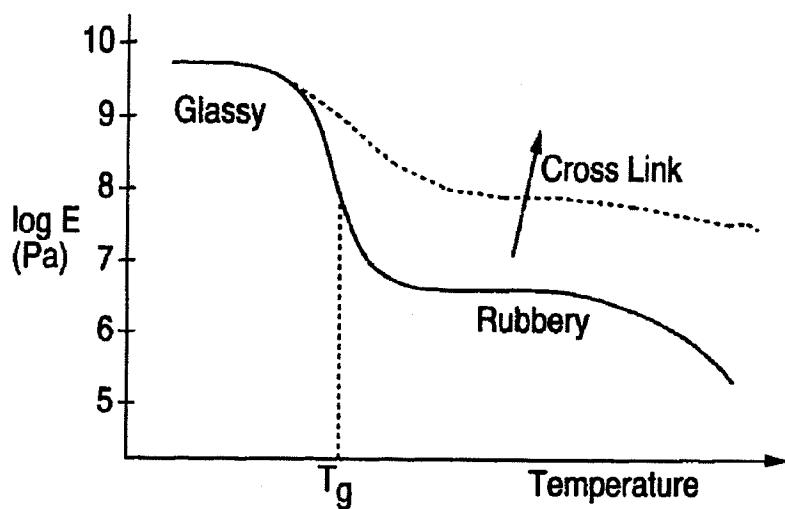


FIG. 3

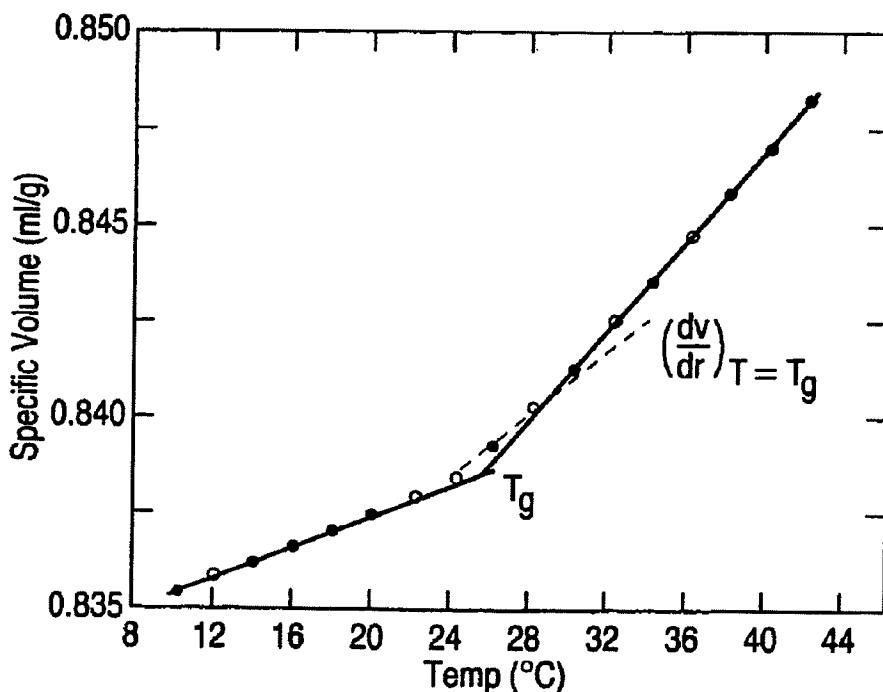


FIG. 4

CORD120659

A1332

U.S. Patent

Oct. 23, 2007

Sheet 4 of 5

US 7,285,304 B1

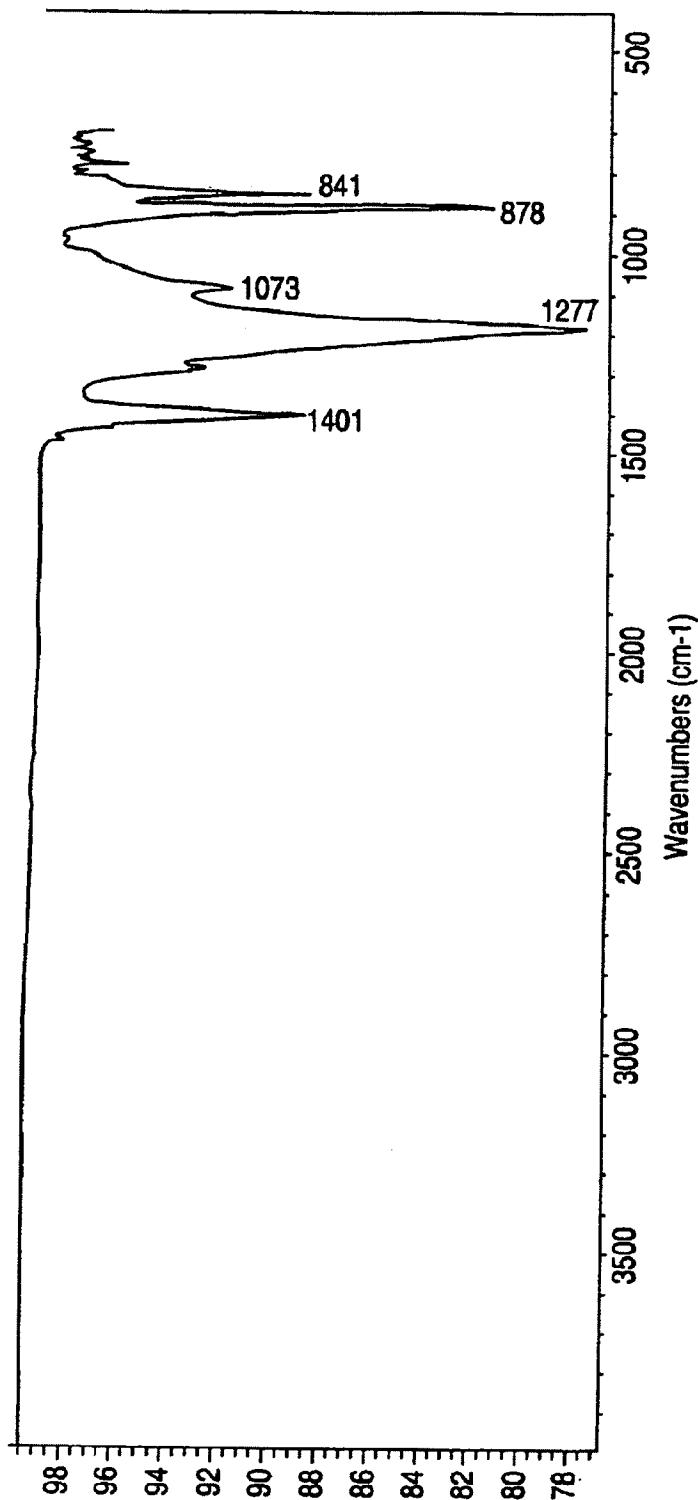


FIG. 5A

CORD120660

A1333

U.S. Patent

Oct. 23, 2007

Sheet 5 of 5

US 7,285,304 B1

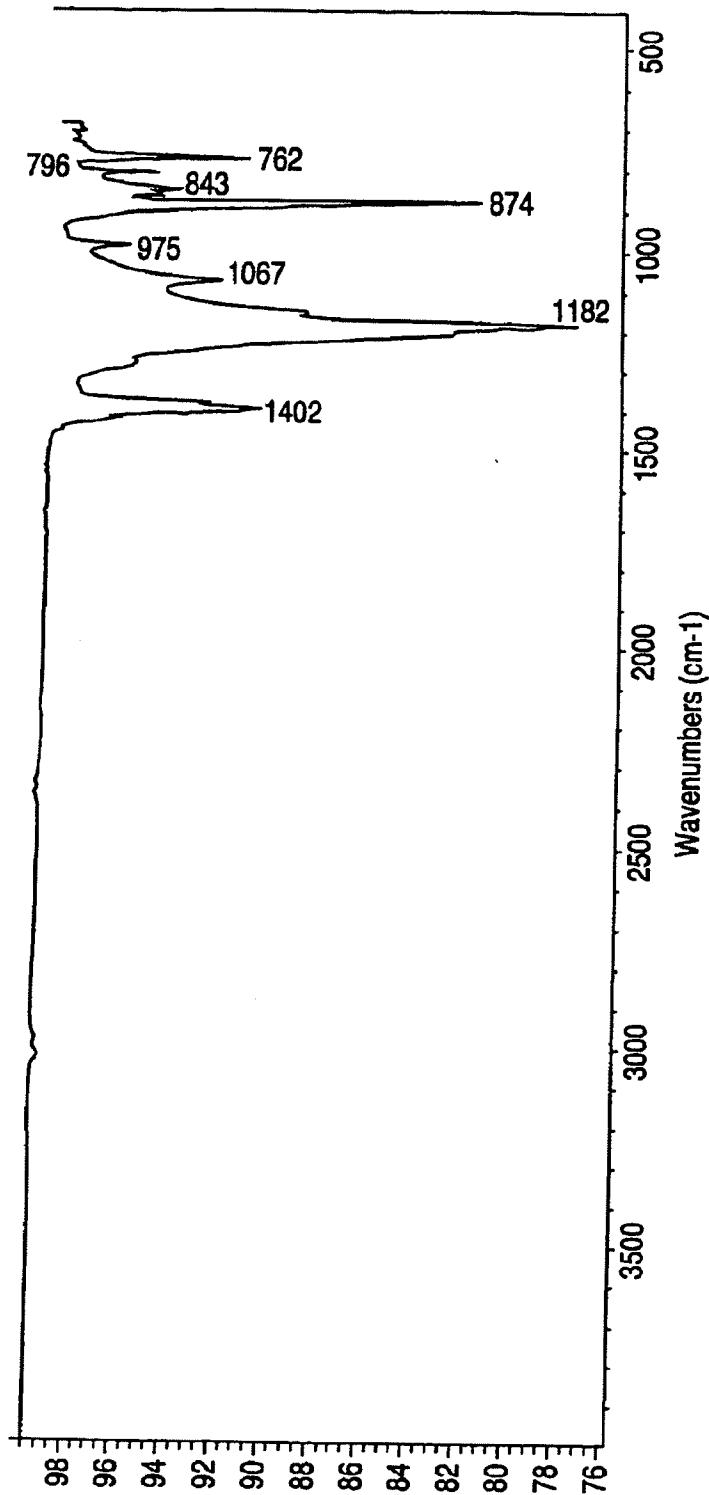


FIG. 5B

CORD120661

A1334

US 7,285,304 B1

1

**FLUID TREATMENT OF A POLYMERIC
COATING ON AN IMPLANTABLE MEDICAL
DEVICE**

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to implantable medical devices, one example of which is a stent. More particularly, the invention relates to a method of coating such implantable medical devices.

2. Description of the Background

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced percutaneously into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned across the occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to remodel the vessel wall. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

A problem associated with the above procedure includes formation of intimal flaps or torn arterial linings, which can collapse and occlude the conduit after the balloon is deflated. Vasospasms and recoil of the vessel wall also threaten vessel closure. Moreover, thrombosis and restenosis of the artery may develop over several months after the procedure, which may necessitate another procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining and to reduce the chance of the development of thrombosis and restenosis a stent is implanted in the lumen to maintain the vascular patency.

Stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically, stents are capable of being compressed so that they can be inserted through small lumens via catheters and then expanded to a larger diameter once they are at the desired location. Mechanical intervention via stents has reduced the rate of restenosis as compared to balloon angioplasty. Yet, restenosis is still a significant clinical problem with rates ranging from 20-40%. When restenosis does occur in the stented segment, its treatment can be challenging, as clinical options are more limited as compared to lesions that were treated solely with a balloon.

Stents are used not only for mechanical intervention but also as vehicles for providing biological therapy. Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or even toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results.

One proposed method of medicating stents involves the use of a polymeric carrier coated onto the surface of the stent. A composition including a solvent, a polymer dissolved in the solvent, and an active agent dispersed in the blend is applied to the stent by immersing the stent in the composition or by spraying the composition onto the stent.

2

The solvent is allowed to evaporate, leaving on the stent strut surfaces a coating of the polymer and the active agent impregnated in the polymer.

5 A potential shortcoming of the foregoing method of medicating stents is that the release rate of the active agent may be too high to provide an efficacious treatment. This shortcoming may be especially pronounced with certain active agents. For instance, it has been found that the release rate of 40-O-(2-hydroxy)ethyl-rapamycin from a standard polymeric coating is greater than 50% in about 24 hours. Thus, there is a need for a coating that reduces the release rate of active agents in order to provide a more efficacious release rate profile.

15 Another shortcoming of the foregoing method of medicating stents is that there can be significant manufacturing inconsistencies. For instance, there can be release rate variability among different stents. It is believed that when some polymers dry on a stent surface to form a coating, 20 different polymer morphologies can develop for different stent coatings, even if the coating process parameters are consistent. The differences in polymer morphology may cause the release rate of the active agent from the polymeric coatings to vary significantly. As a consequence of the inconsistent release rate profiles among stents, there can be 25 clinical complications. Additionally, when stents are stored, the release rate from the stent coating can change during the storage time, known as "release rate drift." Thus, there is a 30 need for a method that reduces the variability of the release rate of active agents among stents and over time. The present invention provides a method and coating to meet the foregoing as well as other needs.

SUMMARY

In accordance with one aspect of the invention, a method of manufacturing an implantable medical device is disclosed including applying a composition to an implantable medical device, the composition including a polymer, an active agent and a solvent; allowing the solvent to evaporate to form a dry coating, the dry coating comprising less than about 2% residual fluid content (w/w); applying a fluid to the dry coating, the fluid being substantially free from any polymer; 40 and allowing the fluid to evaporate from the coating. In one embodiment, the fluid is substantially free from any active agents. In another embodiment, applying the fluid includes spraying the fluid onto the coating or immersing the device into a bath of fluid. In a further embodiment, the temperature of the fluid is equal to or greater than the glass transition 45 temperature of the polymer.

In accordance with a further aspect of the present invention, a method of manufacturing a stent coating is disclosed including applying a composition to a stent, the composition including a semicrystalline polymer and a solvent; allowing the solvent to evaporate to form a dry coating, the dry coating comprising less than about 2% residual fluid content (w/w); and exposing the coating to a fluid for a sufficient duration to increase the crystallinity of the polymer in at 50 least a portion of the coating, the fluid being substantially free from any polymer. In one embodiment, the polymer comprises an ethylene vinyl alcohol copolymer or poly(vinylidene fluoride-co-hexafluoropropene). In another embodiment, exposing the coating to a fluid includes immersing the stent into a bath of fluid. In yet another embodiment, the stent is immersed for about 30 minutes to 55 about twelve hours.

CORD120662

US 7,285,304 B1

3

BRIEF DESCRIPTION OF THE FIGURES

FIGS. 1A-1E illustrate coatings deposited over an implantable medical substrate in accordance with various embodiments of the present invention;

FIG. 2 is a graph of the relationship of heat capacity versus temperature for a polymer;

FIG. 3 is graph of the relationship of elasticity versus temperature for a polymer;

FIG. 4 is a graph of the relationship of specific volume versus temperature for a polymer; and

FIGS. 5A and 5B are Fourier Transform Infrared spectrographs that are referred to in Example 4.

DETAILED DESCRIPTION

Coating

Herein is disclosed a method of manufacturing a drug eluting implantable device, such as a stent, by using a fluid treatment process. The method includes applying a fluid to a dry polymeric coating. The coating can include one or more active agents dispersed within one or more polymers. The active agent can be any substance capable of exerting a therapeutic or prophylactic effect. "Polymer," "poly," and "polymeric" are inclusive of homopolymers, copolymers, terpolymers etc., including random, alternating, block, cross-linked, blends and graft variations thereof.

Some of embodiments of the polymeric coating are illustrated by FIGS. 1A-1E. The Figures have not been drawn to scale, and the thickness of the various layers have been over or under emphasized for illustrative purposes.

Referring to FIG. 1A, a body of a medical substrate 20, such as a stent, is illustrated having a surface 22. A reservoir layer 24 having a polymer and an active agent (e.g., 40-O-(2-hydroxy)ethyl-rapamycin) dispersed in the polymer is deposited on surface 22. The polymer in reservoir layer 24 can be a homopolymer, copolymer, terpolymer, etc. and can include random, alternating, block, cross-linked, blends and graft variations thereof. Reservoir layer 24 can release the active agent when medical substrate 20 is inserted into a biological lumen.

Referring to FIG. 1B, medical substrate 20 includes cavities or micro-pores 26 formed in the body for releasably containing an active agent, as illustrated by dotted region 28. A barrier layer or rate-reducing membrane 30 including a polymer is disposed on surface 22 of medical substrate 20, covering cavities 26. Barrier layer 30 functions to reduce the rate of release of an active agent from medical substrate 20.

Referring to FIG. 1C, medical substrate 20 is illustrated having active-agent-containing or reservoir layer 24 deposited on surface 22. Barrier layer 30 is formed over at least a selected portion of reservoir layer 24.

Referring to FIG. 1D, reservoir coating 24 is deposited on a primer layer 32. Barrier layer 30 is formed over at least a portion of reservoir layer 24. Primer layer 32 serves as an intermediary layer for increasing the adhesion between reservoir layer 24 and surface 22. Increasing the amount of active agent admixed within the polymer can diminish the adhesiveness of reservoir layer 24 to surface 22. Accordingly, using an active agent-free polymer as an intermediary primer layer 32 allows for a higher active agent content for reservoir layer 24.

FIG. 1E illustrates medical substrate 20 having a first reservoir layer 24A disposed on a selected portion of surface 22 of medical substrate 20. First reservoir layer 24A contains a first active agent, e.g., 40-O-(2-hydroxy)ethyl-rapamycin.

4

A second reservoir layer 24B can also be disposed on surface 22. Second reservoir layer 24B contains a second active agent, e.g., taxol. First and second reservoir layers 24A and 24B are covered by first and second barrier layers 30A and 30B, respectively. One of ordinary skill in the art can appreciate that barrier layer 30 can be deposited only on selected areas of reservoir layer 24 so as to provide a variety of selected release parameters. Such selected patterns may become particularly useful if a combination of active agents are used, each of which requires a different release parameter.

By way of example, and not limitation, the impregnated reservoir layer 24 can have a thickness of about 0.1 microns to about 20 microns, more narrowly about 0.5 microns to 10 microns. The particular thickness of reservoir layer 24 is based on the type of procedure for which medical substrate 20 is employed and the amount of the active agent to be delivered. The amount of the active agent to be included on medical substrate 20 can be further increased by applying a plurality of reservoir layers 24 on top of one another. Barrier layer 30 can have any suitable thickness, as the thickness of barrier layer 30 is dependent on parameters such as, but not limited to, the desired rate of release and the procedure for which the stent will be used. For example, barrier layer 30 can have a thickness of about 0.1 to about 10 microns, more narrowly from about 0.25 to about 5 microns. Primer layer 32 can have any suitable thickness, examples of which can be in the range of about 0.1 to about 10 microns, more narrowly about 0.1 to about 2 microns.

Fluid Treatment of the Coating

The implantable medical device manufactured in accordance with embodiments of the present invention may be any suitable medical substrate that can be implanted in a human or veterinary patient. In the interests of brevity, methods of manufacturing a drug eluting stent are described herein. However, one of ordinary skill in the art will understand that other medical substrates can be manufactured using the methods of the present invention.

As noted above, the method of the present invention includes applying a fluid to a dry polymeric coating. A stent having a dry polymeric coating can be provided for the fluid treatment process. Alternatively, the dry polymeric coating can be formed on the stent surface as described in further detail herein. The coatings illustrated in FIGS. 1A-1E, for example, can be exposed to the fluid treatment process.

"Dry coating" is defined as a coating with less than about 10% residual fluid (e.g., solvent(s) or water) content (w/w). In one embodiment, the coating has less than about 2% residual fluid content (w/w), and more narrowly, less than about 1% residual fluid content (w/w). The amount of residual fluids in the coating can be determined by a Karl Fisher, or ThermoGravimetric Analysis (TGA), study. For example, a coated stent can be placed in the TGA instrument, and the weight change can be measured at 100° C. as an indication of water content, or measured at a temperature equal to the boiling temperature of the solvent used in the coating as an indication of the solvent content.

"Fluid" is defined as a liquid, vapor or a combination of liquids and/or vapors (i.e., mixture of two or more fluids) that is completely or substantially free from a polymeric substance. In one embodiment, the fluid comprises one or more active agents or drugs. In another embodiment, the fluid is also completely or substantially free from any active agents or drugs. "Substantially free" means that there is more fluid than the other substance (i.e., polymer and/or

CORD120663

US 7,285,304 B1

5

drug and/or other ingredient) (w/w). In one embodiment, the fluid has less than 0.05% of the substance (i.e., polymer and/or drug and/or other ingredient) (w/w), more narrowly less than 0.01% (w/w) of the substance. "Completely" means that the fluid has 0% (w/w) of such substances.

In one embodiment, the dry coating is subjected to the fluid treatment by applying the fluid to the coating to modify the release rate of the active agent from the coating. In one embodiment, the liquid phase of the fluid should act as or be a solvent for the active agent in the coating by at least partially dissolving the active agent. "Solvent" is defined as a substance capable of dissolving or dispersing one or more other substances or capable of at least partially dissolving or dispersing the substance(s) to form a uniformly dispersed mixture at the molecular- or ionic-size level. When acting as a solvent for the active agent, in one embodiment, the liquid phase of the fluid can be capable of dissolving at least about 5 mg of the active agent in about 1 L of the liquid phase of the fluid at ambient pressure and temperature, and more narrowly, at least about 50 mg of the active agent in about 1 L of the liquid phase of the fluid at ambient pressure and temperature.

Particular polymer and fluid combinations can be selected to desirably affect the polymer morphology and/or drug distribution within the coating in order to modify the release rate of the active agent. For instance, a particular polymer and fluid combination can be selected to cause the polymer in the dry coating to swell as described in Examples 2-4 below. It is also possible to select a combination that advantageously causes the polymer to partially dissolve on the coating. A volatile fluid that partially dissolves the polymer can be used to form a thin membrane of the polymer on the surface of the coating that is substantially free of the active agent.

If the fluid causes the polymer to partially dissolve, the fluid used for the process and the process parameters can be selected to prevent the removal of the polymer from the coating. For example, a fluid can be selected that is a more effective solvent for the active agent than the polymer to prevent the polymer from being removed from the coating. Therefore, some of the active agent can be dissolved in the fluid before the polymer is washed away from the coating. In addition, a volatile fluid, e.g., a fluid having a liquid phase with a boiling temperature below 60° C. at atmospheric pressure, can be selected to prevent the polymer from being removed from the coating.

The fluid treatment can be beneficial because, without the fluid treatment, the active agent (e.g., 40-O-(2-hydroxy)ethyl-rapamycin) can diffuse from the polymer matrix at a rate that could be too high for certain clinical conditions. For example, by using the process of the present invention, a fluid can be applied to the dry coating for a sufficient duration effective to decrease the release rate of 40-O-(2-hydroxy)ethyl-rapamycin, or analog or derivative thereof, by about 50% as compared to a control group, as demonstrated in Example 3 below.

Without being bound by any particular theory, it is believed that the diffusion rate of the active agent from the polymer of the present invention can be modified because the fluid treatment modifies the polymer morphology and/or redistributes the solid state concentration of the active agent within the dry coating. For example, in one embodiment of the present invention, the fluid used for the treatment causes the polymer in the coating to swell, and at the same time, solubilizes the active agent in the coating. The fluid therefore extracts a portion of the active agent from the surface layer of the coating, and causes the polymer to redistribute

6

at the surface of the coating to form a thin membrane on the surface that is substantially free of the active agent. The thin membrane of the polymer at the surface can reduce the release rate of the active agent from the deeper regions in the final coating.

In another embodiment of the present invention, the dry coating is subjected to a fluid treatment by applying a pure fluid to the coating for a sufficient duration to increase the percent crystallinity of the polymer in the coating. Methods of determining the percent crystallinity of the polymer are described below.

By increasing the percent crystallinity of the polymer in the coating, the fluid treatment process can address some of the shortcomings of conventional coating techniques. For instance, the diffusion rate of the active agent from the polymer of the present invention, for example, can be modified by selecting a fluid which increases the percent crystallinity of the polymer in the coating without substantially extracting the drug.

By increasing the percent crystallinity of the polymer in the coating, the fluid treatment process of the present invention can also increase the manufacturing consistency of drug eluting stents by reducing the variability of the release rate of active agents among stents. By exposing a stent coating to a fluid treatment process, for example, it is believed that the standard deviation of the mean release rate of the active agent in a 24 hour period can be decreased so that the standard deviation is lower than the standard deviation of the mean release rate for a baseline group of stents (i.e., stents which have not been subjected to a fluid treatment process).

Without being bound by any particular theory, it is believed that the fluid treatment process can increase manufacturing consistency by moving a polymeric stent coating closer to a kinetic or thermodynamic equilibrium. For example, typically if a semicrystalline polymer is employed in the coating composition, when volatile solvents are used in the coating composition, the polymer does not have an opportunity to fully crystallize before the solvent is removed to form the dry coating. The fluid treatment process can be used to improve polymer morphology by increasing the percent crystallinity of the polymer.

The fluid treatment process can also reduce the release rate drift over time by increasing the percent crystallinity of the polymer in the coating. "Release rate drift" refers to the phenomenon in which the release rate of an active agent from a polymeric coating can change over time, for instance while the stent is in storage. Release rate drift may occur because of changes in the morphology of a polymeric coating over a period of time, for example if the polymeric coating is exposed to degradation agents such as oxygen and moisture. The fluid treatment process can increase the percent crystallinity of the polymer so that the polymer is in a thermodynamically or kinetically stable state, thereby reducing the changes in the morphology of a polymeric coating over time. The solvent treatment process, therefore, can improve the self life of the stent product.

"Percent crystallinity" refers to the percentage of the polymer material that is in a crystalline form. In one embodiment of the present invention, the polymer is a semicrystalline polymer having between 10 and 75 percent crystallinity. For example, poly(vinylidene fluoride-co-hexafluoroisopropylene) can achieve about 20% crystallinity when the vinylidene fluoride to hexafluoroisopropylene ratio is 85:15. Also, by example, poly(vinylidene fluoride) can achieve about a 65 percent crystallinity, and poly(6-aminocaproic acid) can achieve about a 64 percent crystallinity.

CORD120664

A1337

US 7,285,304 B1

7

Those of ordinary skill in the art understand that there are several methods for determining the percent crystallinity in polymers. These methods are, for example, described in L. H. Sperline, Introduction to Physical Polymer Science (3rd ed. 2001). The first involves the determination of the heat of fusion of the whole sample by calorimetric methods. The heat of fusion per mole of crystalline material can then be estimated independently by melting point depression experiments. The percent crystallinity is then given by heat of fusion of the whole sample divided by the heat of fusion per mole of crystalline material times 100.

A second method involves the determination of the density of the crystalline portion via X-ray analysis of the crystal structure, and determining the theoretical density of a 100% crystalline material. The density of the amorphous material can be determined from an extrapolation of the density from the melt to the temperature of interest. Then the percent crystallinity is given by:

$$\% \text{ Crystallinity} = \frac{\rho_{\text{expt}} - \rho_{\text{amorph}}}{\rho_{100\% \text{ cryst}} - \rho_{\text{amorph}}} \times 100$$

where ρ_{expt} represents the experimental density, and ρ_{amorph} and $\rho_{100\% \text{ cryst}}$ are the densities of the amorphous and crystalline portions, respectively.

A third method stems from the fact that X-ray diffraction depends on the number of electrons involved and is thus proportional to the density. Besides Bragg diffraction lines for the crystalline portion, there is an amorphous halo caused by the amorphous portion of the polymer. The amorphous halo occurs at a slightly smaller angle than the corresponding crystalline peak, because the atomic spacings are larger. The amorphous halo is broader than the corresponding crystalline peak, because of the molecular disorder. This third method can be quantified by the crystallinity index, CI, where

$$CI = \frac{A_c}{A_a + A_c}$$

and where A_c and A_a represent the area under the Bragg diffraction line and corresponding amorphous halo, respectively.

Representative examples of fluids for the treatment process include chloroform, acetone, water (buffered saline), dimethylsulfoxide, propylene glycol methyl ether, iso-propylalcohol, n-propylalcohol, methanol, ethanol, tetrahydrofuran, dimethylformamide, dimethylacetamide, benzene, toluene, xylene, hexane, cyclohexane, pentane, heptane, octane, nonane, decane, decalin, ethyl acetate, butyl acetate, isobutyl acetate, isopropyl acetate, butanol, diacetone alcohol, benzyl alcohol, 2-butanone, cyclohexanone, dioxane, methylene chloride, carbon tetrachloride, tetrachloroethylene, tetrachloro ethane, chlorobenzene, 1,1,1-trichloroethane, formamide, hexafluoroisopropanol, 1,1,1-trifluoroethanol, acetonitrile, and hexamethyl phosphoramide and a combination thereof.

The fluid can be applied by immersing the stent in the fluid. The stent can be immersed in the fluid, for example, for about ten seconds to about thirteen hours, more narrowly about 30 minutes to about twelve hours. The stent should be

8

immersed for a sufficient duration to effect the desired changes in the polymer morphology and/or drug distribution.

The fluid can also be applied by spraying the fluid onto the stent with a conventional spray apparatus, or applied by other metering devices. For instance, the stent can be sprayed for one to ten spray cycles (i.e., back and forth passes along the length of the stent) using a spray apparatus to deposit about 1 ml to about 500 ml, more narrowly 5 ml to about 20 ml, of the fluid onto the stent. The spray process can take place in a vacuum chamber at a reduced pressure (e.g., less than 300 mm Hg) in order to raise the fluid concentration in the vapor phase. As above, the stent should be exposed to the fluid spray process for a sufficient duration to effect the desired changes in the polymer morphology.

The fluid treatment should not adversely affect the characteristics of the active agent present in the coating. In order to prevent possible degradation of the active agents or the polymers in the coating, the fluid should not react with the active agent in the coating. Additionally, the fluid should not cause the active agent to crystallize within the dry polymeric coating. Crystallization of the active agent may disadvantageously change the release rate of the active agent from the coating when implanted into a biological lumen.

Subsequent to the fluid treatment process, the coating should be allowed to dry to substantially remove the fluid. For instance, the removal of the fluid can be induced by baking the stent in an oven at a mild temperature (e.g., 60° C.) for a suitable duration of time (e.g., 2-4 hours).

In one embodiment of the present invention, the fluid treatment is directed to selected portions of the drug eluting stent. By directing the fluid treatment to only portions of the stent coating, the stent coating can have a variable drug release profile, for example along the length of the stent. For instance, the release rate at the end segments of the stent can be reduced relative to the release rate from middle segment of the stent by applying the fluid only to the end segments of the stent.

The fluid treatment process parameters are selected to limit the penetration of the fluid into the thickness of the coating. By limiting the treatment process, a coating can be produced in which the shallower regions of the coating have a different coating morphology than the deeper regions. For example, a volatile fluid (e.g., acetone) or a limited process duration can be used so that most of the fluid is evaporated before penetrating into the deep regions of the coating. One of ordinary skill in the art will understand that the fluids chosen or the duration of the fluid treatment will depend on factors such as the desired diffusion rate of the active agent through the polymer, and the inherent characteristics of the polymers and active agents used in the coating.

In another embodiment of the present invention, the fluid used for the treatment is heated to a temperature greater than room temperature as the fluid is applied to the polymeric coating. The temperature used should be below the temperature that significantly degrades the active agent disposed in the coating.

In one embodiment, the polymer in the coating is a semicrystalline polymer (e.g., polyvinyl chloride or an ethylene vinyl alcohol copolymer), and the fluid is heated to the crystallization temperature (T_c) of the polymer as the fluid is applied to the polymeric coating. "Crystallization temperature" refers to the temperature at which a semicrystalline polymer has its highest percent crystallinity. Amorphous polymers do not exhibit a crystallization temperature. Methods of determining a crystallization temperature are described below. The crystallization temperature of ethylene

CORD120665

US 7,285,304 B1

9

vinyl alcohol copolymer (44 mole % ethylene), for instance, is about 415° K (ethylene vinyl alcohol copolymer ("EVAL") is commonly known by the generic name EVOH or by the trade name EVAL). Other examples of crystallization temperatures include 396° K for poly(ethylene terephthalate) as measured by differential scanning calorimetry (as reported by Parravicini et al., *J. Appl. Polym. Sci.*, 52(7), 875-85 (1994); and 400° K for poly(p-phenylene sulfide) as measured by differential scanning calorimetry (as reported by Ding et al. *Macromolecules*, 29(13), 4811-12 (1996)).

In another embodiment of the present invention, the fluid applied to the dry polymeric coating is heated so that the dry coating is exposed to a temperature equal to or greater than the T_g of the polymer in the coating. Both amorphous and semicrystalline polymers exhibit glass transition temperatures. Additionally, if the polymer is a semicrystalline polymer, the dry polymeric coating can be exposed to a temperature equal to or greater than the T_g but less than the melting temperature (T_m) of the polymer in the coating. Amorphous polymers do not exhibit a T_m .

The T_g is the temperature at which the amorphous domains of a polymer change from a brittle vitreous state to a plastic state at atmospheric pressure. In other words, the T_g corresponds to the temperature where the onset of segmental motion in the chains of the polymer occurs. When an amorphous or semicrystalline polymer is exposed to an increasing temperature, the coefficient of expansion and the heat capacity of the polymer both increase as the temperature is raised, indicating increased molecular motion. As the temperature is raised the actual molecular volume in the sample remains constant, and so a higher coefficient of expansion points to an increase in free volume associated with the system and therefore increased freedom for the molecules to move. The increasing heat capacity corresponds to an increase in heat dissipation through movement.

T_g of a given polymer can be dependent on the heating rate and can be influenced by the thermal history of the polymer. Furthermore, the chemical structure of the polymer heavily influences the glass transition by affecting mobility. Generally, flexible main-chain components lower the T_g ; bulky side-groups raise the T_g ; increasing the length of flexible side-groups lowers the T_g ; and increasing main-chain polarity increases the T_g . Additionally, the presence of crosslinking polymeric components can increase the observed T_g for a given polymer. For instance, FIG. 3 illustrates the effect of temperature and crosslinking on the modulus of elasticity of a polymer, showing that forming cross-links in a polymer can increase the T_g and shift the elastic response to a higher plateau-one that indicates that the polymer has become more glassy and brittle. Moreover, molecular weight can significantly influence T_g , especially at lower molecular weights where the excess of free volume associated with chain ends is significant.

The T_m of a polymer, on the other hand, is the temperature at which the last trace of crystallinity in a polymer disappears as a sample is exposed to increasing heat. The T_m of a polymer is also known as the fusion temperature (T_f). The T_m is always greater than the T_g for a given polymer.

Like the T_g , the melting temperature of a given polymer is influenced by the structure of the polymer. The most influential inter- and intramolecular structural characteristics include structural regularity, bond flexibility, close-packing ability, interchain attraction. In general, high melting points are associated with highly regular structures, rigid molecules, close-packing capability, strong interchain attraction, or two or more of these factors combined.

10

Referring to FIG. 2, if the coating polymer is a semicrystalline polymer, as the polymeric coating is exposed to an increasing temperature, the polymer exhibits three characteristic thermal transitions represented by first curve 60, second curve 62 and third curve 64. FIG. 2 illustrates the change in heat capacity (endothermic v. exothermic) of a semicrystalline polymer as the polymer is exposed to an increasing temperature, as measured by the differential scanning calorimetry (DSC) method. DSC uses the relationship between heat capacity and temperature as the basis for determining the thermal properties of polymers and is further described below.

By way of illustration, when a semicrystalline polymer is exposed to an increasing temperature, the crystallinity of the polymer begins to increase as the increasing temperature reaches the T_g . At and above the T_g , the increased molecular motion of the polymer allows the polymer chains to move around more to adopt a more thermodynamically stable relationship, and thereby increase the percent crystallinity of the polymer sample. In FIG. 2, the T_g is shown as point T_g of first curve 60, which is the temperature at which half of the increase in heat capacity (ΔC_p) has occurred. The percent crystallinity then increases rapidly after point T_g and is maximized at the T_c of the polymer, which is indicated at the point T_c (the apex of second curve 62). As the temperature continues to increase, the temperature approaches the melting temperature (T_m) of the polymer, and the percent crystallinity decreases until the temperature reaches the melting temperature of the polymer (at point T_m of curve 64). As noted above, T_m is the temperature where the last trace of crystallinity in the polymer disappears. The heat of crystallization, ΔH_c , and the heat of fusion, ΔH_f , can be calculated as the areas under curves 62 and 64. The heat of crystallization and heat of fusion must be equal, but with opposite signs.

The T_g and/or the T_m of the polymer that is to be exposed to the fluid treatment should be determined experimentally in order to determine which temperatures can be used to treat the dry polymeric coating with the heated fluid. As used herein, "test polymer" means the polymer that is measured to determine the T_g and/or the T_m of the polymer. "Coating polymer" means the polymer that is actually applied as a component of the stent coating.

In order to accurately characterize the thermal properties of the coating polymer, one should consider the number of factors that can influence the T_g and T_m of a polymer. In particular, the factors include (1) the structure of the polymer (e.g., modification of side groups and dissimilar stereoregularity); (2) the molecular weight of the polymer; (3) the molecular-weight distribution (M_w/M_n) of the polymer; (4) the crystallinity of the polymer; (5) the thermal history of the polymer; (6) additives or fillers that are included in the polymer; (7) the pressure applied to the polymer as the polymer is heated; (8) residual fluids in the polymer and (9) the rate that the polymer is heated.

One can account for the foregoing factors by using a test polymer that is substantially the same as the coating polymer, and is tested under substantially the same conditions as the conditions used to conduct the fluid treatment of the polymeric coating. The test polymer should have the same chemical structure as the coating polymer, and should have substantially the same molecular weight and molecular-weight distribution as the coating polymer. For example, if the polymer is a blend of copolymers or homopolymers, the test polymer should have substantially the same percentage of components as the coating polymer. At the same time, the test polymer should have substantially the same crystallinity

CORD120666

US 7,285,304 B1

11

as the coating polymer. Methods of determining crystallinity are discussed herein. Additionally, the composition used to form the test polymer should include the same compounds (e.g., additives such as therapeutic substances) and liquids (e.g., solvent(s) and water) that are mixed with the coating polymer. Moreover, the test polymer should have the same thermal history as the coating polymer. The test polymer should be prepared under the same conditions as the coating polymer, such as using the same solvent, temperature, humidity and mixing conditions. Finally, the heating rate used for measuring the transition temperature of the test polymer should be substantially similar to the heating rate used to conduct the fluid treatment of the polymeric coating.

The T_g and T_m of the test polymer can be measured experimentally by testing a bulk sample of the polymer. As understood by one of ordinary skill in the art, a bulk sample of the polymer can be prepared by standard techniques, for example those that are outlined in the documentation accompanying the instruments used to measure the transition temperature of the polymer.

There are several methods that can be used to measure the T_g and T_m of a polymer. The T_g and T_m can be observed experimentally by measuring any one of several basic thermodynamic, physical, mechanical, or electrical properties as a function of temperature. Methods of measuring glass transition temperatures and melting temperatures are understood by one of ordinary skill in the art and are discussed by, for example, L. H. Sperling, Introduction to Physical Polymer Science, Wiley-Interscience, New York (3rd ed. 2001), and R. F. Boyer, in Encyclopedia of Polymer Science and Technology, Suppl. Vol. 2, N. M. Bikales, ed., Interscience, New York (1977).

The T_g of a bulk sample can be observed by measuring the expansion of the polymer as the polymer is exposed to increasing temperature. This process is known as dilatometry. There are two ways of characterizing polymers via dilatometry. One way is to measure the linear expansivity of the polymer sample. Another method involves performing volume-temperature measurements, where the polymer is confined by a liquid and the change in volume is recorded as the temperature is raised. The usual confining liquid is mercury, since it does not swell organic polymers and has no transition of its own through most of the temperature range of interest. The results may be plotted as specific volume versus temperature as shown in FIG. 4, which illustrates a representative example of a dilatometric study of branched poly(vinyl acetate). Since the elbow in volume-temperature studies is not sharp (measurements of T_g using dilatometric studies show a dispersion of about 20-30° C.), the two straight lines below and above the transition are extrapolated until they meet. The extrapolated meeting point is taken as the T_g . A representative example of an apparatus that can be used to measure a T_g via dilatometric studies is the Dilatometer DIL 402 PC (available from Netzsch, Inc., Exton, Pa.).

Thermal methods can also be used to measure the T_g of a bulk sample. Two closely related methods are differential thermal analysis (DTA), and differential scanning calorimetry (DSC). Both methods yield peaks relating to endothermic and exothermic transitions and show changes in heat capacity. A representative example of a DTA apparatus is the Rheometrics STA 1500 which provides simultaneous thermal analysis via DTA and DSC.

In addition to the information that can be produced by a DTA, the DSC method also yields quantitative information relating to the enthalpic changes in the polymer (the heat of fusion of the temperature, ΔH_f). The DSC method uses a servo system to supply energy at a varying rate to the sample

12

and the reference, so that the temperatures of the two stay equal. The DSC output plots energy supplied against average temperature. By this method, the areas under the peaks can be directly related to the enthalpic changes quantitatively.

Referring to FIG. 2, the T_g can be taken as the temperature at which one-half of the increase in the heat capacity, ΔC_p , has occurred. The increase in ΔC_p is associated with the increased molecular motion of the polymer.

A method of separating a transient phenomenon such as a hysteresis peak from the reproducible result of the change in heat capacity is obtained via the use of modulated DSC. Here, a sine wave is imposed on the temperature ramp. A real-time computer analysis allows a plot of not only the whole data but also its transient and reproducible components. Representative examples of modulated DSC apparatuses are those in the Q Series™ DSC product line from TA Instruments, New Castle, Del.

Another representative example of an apparatus that uses DSC as the base technology for measuring the T_g is a micro thermal analyzer, such as the μ TA™ 2990 product from TA Instruments. A micro thermal analyzer can have an atomic force microscope (AFM) that is used in conjunction with a thermal analyzer. The instrument can be used to analyze individual sample domains identified from the AFM images. In a micro thermal analyzer such as the μ TA™ 2990, the AFM measurement head can contain an ultra-miniature probe that functions as a programmable heat source and temperature sensor. A micro thermal analyzer, therefore, can provide information similar to that from traditional thermal analysis, but on a microscopic scale. For example, the μ TA™ 2990 can provide images of a sample in terms of its topography, relative thermal conductivity and relative thermal diffusivity. The μ TA™ 2990 can also provide spatial resolution of about 1 μm with a thermal probe and atomic resolution with regular AFM probes. Other advantages of the μ TA™ 2990 is that it can heat the polymer sample from ambient to about 500° C. at heating rates up to 1500° C./minute which allows for rapid thermal characterization (e.g., in less than 60 seconds), and it can hold the sample isothermally over a broad range of temperatures (e.g., -70 to 300° C.), which allows for thermal characterization over a broad temperature range.

Since the notion of the glass-rubber transition stems from a softening behavior, mechanical methods can provide very direct determination of the T_g for a bulk sample. Two fundamental types of measurement prevail: the static or quasi-static methods, and the dynamic methods. For amorphous polymers and many types of semicrystalline polymers in which the crystallinity does not approach 100%, stress relaxation, Gehman, and/or Glash-Berg instrumentation provide, through static measurement methods, rapid and inexpensive scans of the temperature behavior of new polymers before going on to more complex methods. Additionally, there are instruments that can be employed to measure dynamic mechanical spectroscopy (DMS) or dynamic mechanical analysis (DMA) behavior. A representative example of an apparatus for a DMA method is the DMA 242, available from Netzsch, Inc., Exton, Pa.

Another method for studying the mechanical spectra of all types of polymers, especially those that are not self-supporting, is torsional braid analysis (TBA). In this case the polymer is dipped onto a glass braid, which supports the sample. The braid is set into a torsional motion. The sinusoidal decay of the twisting action is recorded as a function of time as the temperature is changed. Because the braid acts

CORD120667

US 7,285,304 B1

13

as a support medium, the absolute magnitudes of the transitions are not obtained; only their temperatures and relative intensities are recorded.

The T_g of a bulk sample of a polymer can also be observed by utilizing electromagnetic methods. Representative examples of electromagnetic methods for the characterization of transitions in polymers are dielectric loss (e.g., using the DEA 2970 dielectric analyzer, available from TA Instruments, New Castle, Del.) and broad-line nuclear magnetic resonance (NMR).

If the thickness of the coating polymer is ultra thin (i.e., less than 1 micron), it may be useful to utilize specialized measuring techniques, at least to compare the results with the values determined by measuring a bulk polymer sample to ensure that the bulk values are not affected by the thickness of the polymer layer. Specialized techniques may be useful because it has recently been observed that the T_g of a polymer can be influenced by the thickness of the polymer layer. Researchers, for example, have observed that polystyrene films on hydrogen-passivated Si had glass transition temperatures that were lower than the bulk value if the thickness of the films was less than 0.04 microns. See Forest et al., Effect of Free Surfaces on the T_g of Thin Polymer Films, Physical Review Letters 77(10), 2002-05 (September 1996).

Brillouin light scattering (BLS) can be used to measure the T_g of a polymer in an ultra thin film. The ultra thin films can be prepared by spin casting the polymer onto a substrate (e.g., the same substrate used to support the coating polymer on the stent). A spinning apparatus is available, for example, from Headway Research, Inc., Garland, Tex. BLS can also be used to find the T_g of a polymer in a bulk sample. In BLS studies of bulk polymers, one measures the velocity v_L of the bulk longitudinal phonon, where $v_L = (C_{11}/\rho)^{1/2}$, C_{11} is the longitudinal elastic constant, and ρ is the density. Since C_{11} is a strong function of ρ , as the sample temperature is changed, the temperature dependence of v_L exhibits an abrupt change in slope at the temperature at which the thermal expansivity is discontinuous, i.e., the T_g . For thin films, BLS probes the elastic properties through observation of film-guided acoustic phonons. The guided acoustic modes are referred to as Lamb modes for freely standing films. For further discussion of the application of BLS for measuring T_g , see Forest et al., Effect of Free Surfaces on the Glass Transition Temperature of Thin Polymer Films, Physical Review Letters 77(10), 2002-05 (September 1996) and Forest et al. Mater. Res. Soc. Symp. Proc. 407, 131 (1996).

The T_g of an ultra thin polymer film can also be determined by using three complementary techniques: local thermal analysis, ellipsometry and X-ray reflectivity. See, e.g., Fryer et al., Dependence of the Glass Transition Temperature of Polymer Films on Interfacial Energy and Thickness, Macromolecules 34, 5627-34 (2001). Using ellipsometry (e.g., with a Rudolph Auto E1 nulling ellipsometer) and X-ray reflectivity (e.g., with a Scintag XDS 2000), the T_g is determined by measuring changes in the thermal expansion of the film. Using local thermal analysis, on the other hand, the T_g is determined by measuring changes in the heat capacity and thermal conductivity of the film and the area of contact between a probe and the polymer surface.

Table 1 lists the T_g for some of the polymers used in the embodiments of the present invention. The cited temperature is the temperature as reported in the noted reference and is provided by way of illustration only and is not meant to be limiting.

14

TABLE 1

POLYMER	T_g (°K)	T_g	METHOD USED TO CALCULATE	REFERENCE
			EVAL	
Poly(n-butyl methacrylate)	293	Dilatometry	Rogers et al., J. Phys. Chem., 61, 985-90 (1957)	
Poly(ethylene-co-(vinyl acetate))	263	DSC and DMA	Scott et al., J. Polym. Sci., Part A, Polym. Chem., 32(3), 539-55 (1994)	
Poly(ethylene terephthalate)	343.69	DSC	Sun et al., J. Polym. Sci., Part A, Polym. Chem., 34(9), 1783-92 (1996)	
Poly(vinylidene fluoride)	243	Dielectric relaxation	Barid et al., J. Mater. Sci., 10(7), 1248-51 (1975)	
Poly(p-phenylene sulfide)	361	DSC	Ding, et al., Macromolecules, 29(13), 4811-12 (1996)	
Poly(6-aminocaproic acid)	325	DSC	Gee et al., Polymer, 11, 192-97 (1970)	
Poly(methyl methacrylate)	367	DSC	Fernandez-Martin, et al., J. Polym. Sci., Polym. Phys. Ed., 19(9), 1353-63 (1981)	
Poly(vinyl alcohol)	363	Dilatometry	Fujii et al., J. Polym. Sci., Part A, 2, 2327-47 (1964)	
Poly(epsilon-caprolactone)	208	DSC	Loegfren et al., Macromolecules, 27(20), 5556-62 (1994)	

As noted above, "polymer" as used herein is inclusive of homopolymers, copolymers, terpolymers etc., including random, alternating, block, cross-linked, blends and graft variations thereof. By using the methods of measurement described above, one may observe more than one T_g for some of these types of polymers. For example, some polymer blends that exhibit two phase systems can have more than one T_g . Additionally, some semicrystalline polymers can have two glass transitions, especially when they have a higher percent crystallinity. See Edith A. Turi, Thermal Characterization of Polymeric Materials, Academic Press, Orlando, Fla. (1981). Bulk-crystallized polyethylene and polypropylene, for example, can have two glass transition temperatures at a relatively high percent crystallinity. The lower of the two transitions is represented as $T_g(L)$, which can be the same as the conventional T_g at zero crystallinity. The higher transition is designated as $T_g(U)$ and becomes more detectable as the crystallinity increases. The difference, $\Delta T_g = T_g(U) - T_g(L)$, tends to approach zero as the fractional crystallinity X approaches zero.

It has also been reported that block and graft copolymers can have two separate glass transition temperatures. For some of these polymers, each T_g can be close to the T_g of the parent homopolymer. The following Table 2 lists the glass transition temperatures for representative examples of block and graft copolymers. As illustrated by Table 2, most of these block and graft copolymers exhibit two glass transition temperatures. The cited temperatures were reported in Black and Worsfold, J. Appl. Polym. Sci., 18, 2307 (1974) who used a thermal expansion technique to measure the temperatures, and are provided by way of illustration only.

CORD120668

A1341

US 7,285,304 B1

15

TABLE 2

M ₁	M ₂	% M ₁	Total MW	Lower T _g (° K)	Upper T _g (° K)
α-Methylstyrene	Vinyl acetate	18	103,000	308	455
α-Methylstyrene	Vinyl chloride	67	39,000	265	455
α-Methylstyrene Styrene	Styrene	45	61,000	400	—
	Methyl methacrylate	40	70,000	—	371
Styrene	Butyl acrylate	46	104,000	218	372
Styrene	Ethylene oxide	50	40,000	201	373
Styrene	Isoprene	50	1,000,000	198	374
Styrene	Isobutylene	40	141,000	204	375
Methyl Methacrylate	Ethyl acrylate	56	162,000	250	388
Methyl Methacrylate	Vinyl acetate	50	96,000	311	371
Methyl Methacrylate	Ethyl methacrylate	50	104,000	342	379

In one embodiment of the present invention, if the polymer exhibits more than one T_g, the fluid is heated to expose the polymer to a temperature equal to or greater than the lowest observed T_g. It is believed that by exposing a polymer to a temperature equal to or greater than the lowest T_g, the release rate of the polymer should be reduced to a measurable extent because at least some of the amorphous domains will be modified during the process. In another embodiment, if the polymer exhibits more than one T_g, the fluid is heated to expose the polymer to a temperature equal to or greater than the highest observed T_g. By exposing the polymer to the highest T_g, it is believed that one can maximize the release rate reduction.

As noted above, in one embodiment, the drug polymeric drug coating can be exposed to a temperature equal to or greater than the T_g lower than the T_m of the polymer. There are several types of methods that can be used to measure the T_m of a polymer. For example, the melting temperature can be observed by measuring visual, physical, and thermal properties as a function of temperature.

T_m can be measured by visual observation by using microscopic techniques. For instance, the disappearance of crystallinity in a semicrystalline or crystalline polymer can be observed with a microscope, with the sample housed between crossed nicols (i.e., an optical material that functions as a prism, separating light rays that pass through it into two portions, one of which is reflected away and the other transmitted). As a polymer sample is heated, the sharp X-ray pattern characteristic of crystalline material gives way to amorphous halos at the T_m.

Another way of observing the T_m is to observe the changes in specific volume with temperature. Since melting constitutes a first-order phase change, a discontinuity in the volume is expected. The T_m should give a discontinuity in the volume, with a concomitant sharp melting point. Because of the very small size of the crystallites in bulk crystallized polymers, however, most polymers melt over a range of several degrees. The T_m is the temperature at which the last trace of crystallinity disappears. This is the temperature at which the largest and/or most "perfect" crystals are melting.

Alternatively, the T_m can be determined by using thermomechanical analysis (TMA) that uses a thermal probe (e.g., available from Perkin Elmer, Norwalk, Conn.). The T_m can also be determined with a thermal-based method. For

16

example, a differential scanning calorimetry (DSC) study can be used to determine the T_m. The same process for DSC as described above for the determination of T_g can be used to determine the T_m. Referring to FIG. 2, the T_m of the representative polymer is the peak of curve 64.

Table 3 lists the melting temperatures for some of the polymers used in the embodiments of the present invention. The cited temperature is the temperature as reported in the noted reference and is provided by way of illustration only and is not meant to be limiting.

TABLE 3

POLYMER	T _m (° K)	METHOD USED TO CALCULATE T _m		REFERENCE
		EVAL	DMA	
Poly(ethylene terephthalate)	526.38	DSC	Tokoh et al., Chem. Express, 2(9), 575-78 (1987)	
Poly(vinylidene fluoride)	444	Dielectric relaxation	Sun et al., J. Polym. Sci., Part A, Polym. Chem., 34(9), 1783-92 (1996)	
Poly(p-phenylene sulfide)	560	DSC	Barid et al., J. Mater. Sci., 10(7), 1248-51 (1975)	
Poly(6-aminocaproic acid)	498	DSC	Ding, et al., Macromolecules, 29(13), 4811-12 (1996)	
Poly(vinyl alcohol)	513	TMA	Gee et al., Polymer, 11, 192-97 (1970)	
Poly(epsilon-caprolactone)	330.5	DSC	Fujii et al., J. Polym. Sci., Part A, 2, 2327-47 (1964)	
			Loefgren et al., Macromolecules, 27(20), 5556-62 (1994)	

In the embodiments of the present invention, the fluid treatment process can be used to reduce the release rate of an active agent from polymeric coatings having various coating structures. Referring to FIG. 1A, for instance, reservoir layer 24 has a polymer and an active agent. The polymer in reservoir layer 24 can be exposed to a fluid sufficient to reduce the release rate of the active agent from reservoir layer 24.

The fluid treatment process can also be directed to a coating having a barrier layer as illustrated in FIGS. 1B-1E. Referring to FIG. 1B, for instance, an active agent can be deposited in cavities 26, and covered by barrier layer 30. In one embodiment of the present invention, the polymer in barrier layer 30 is subjected to the fluid treatment process.

Forming an Active Agent-Containing Coating

The composition containing the active agent can be prepared by first forming a polymer solution by adding a predetermined amount of a polymer to a predetermined amount of a compatible solvent. The polymer can be added to the solvent at ambient pressure and under anhydrous atmosphere. If necessary, gentle heating and stirring and/or mixing can be employed to effect dissolution of the polymer into the solvent, for example 12 hours in a water bath at about 60° C.

Sufficient amounts of the active agent can then be dispersed in the blended composition of the polymer and the solvent. The active agent should be in true solution or saturated in the blended composition. If the active agent is not completely soluble in the composition, operations including mixing, stirring, and/or agitation can be employed

CORD120669

US 7,285,304 B1

17

to effect homogeneity of the residues. The active agent can also be first added to a compatible solvent prior to admixing with the composition.

The polymer can comprise from about 0.1% to about 35%, more narrowly from about 0.5% to about 20% by weight of the total weight of the composition, the solvent can comprise from about 59.9% to about 99.8%, more narrowly from about 79% to about 99% by weight of the total weight of the composition, and the active agent can comprise from about 0.1% to about 40%, more narrowly from about 1% to about 9% by weight of the total weight of the composition. Selection of a specific weight ratio of the polymer and solvent is dependent on factors such as, but not limited to, the material from which the device is made, the geometrical structure of the device, and the type and amount of the active agent employed.

Representative examples of polymers that can be combined with the active agent for the reservoir layer include ethylene vinyl alcohol copolymer (commonly known by the generic name EVOH or by the trade name EVAL); polybutylmethacrylate; poly(ethylene-co-vinyl acetate); poly(vinylidene fluoride-co-hexafluoropropene); poly(hydroxyvalerate); poly(L-lactic acid); poly(epsilon-caprolactone); poly(lactide-co-glycolide); poly(hydroxybutyrate); poly(hydroxybutyrate-co-valerate); polydioxanone; polyorthoester; polyanhydride; poly(glycolic acid); poly(D, L-lactic acid); poly(glycolic acid-co-trimethylene carbonate); polyphosphoester; poly-phosphoester urethane; poly(amino acids); cyanoacrylates; poly(trimethylene carbonate); poly(iminocarbonate); co-poly(ether-esters) (e.g. PEO/PLA); polyalkylene oxalates; polyphosphazenes; biomolecules, such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid; polyurethanes; silicones; polyesters; polyolefins; polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers; vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile; polyvinyl ketones; polyvinyl aromatics, such as polystyrene; polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins; polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins; polyurethanes; rayon; rayon-triacetate; cellulose acetate; cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; and carboxymethyl cellulose.

EVAL is functionally very suitable choice of polymer. EVAL copolymer refers to copolymers comprising residues of both ethylene and vinyl alcohol monomers. One of ordinary skill in the art understands that ethylene vinyl alcohol copolymer may also be a terpolymer so as to include small amounts of additional monomers, for example less than about five (5) mole percentage of styrenes, propylene, or other suitable monomers. Ethylene vinyl alcohol copolymers are available commercially from companies such as Aldrich Chemical Company, Milwaukee, Wis., or EVAL Company of America, Lisle, Ill., or can be prepared by conventional polymerization procedures that are well known to one of ordinary skill in the art.

Poly(butylmethacrylate) ("PBMA") and ethylene-vinyl acetate copolymers can also be especially suitable polymers

18

for the reservoir layer. In one embodiment, the polymer in the reservoir coating is a mixture of PBMA and an ethylene-vinyl acetate copolymer.

KRATON G-1650 is also a suitable polymer. KRATON is manufactured by Shell Chemicals Co. of Houston, Tex., and is a three block copolymer with hard polystyrene end blocks and a thermoplastic elastomeric poly(ethylene-butylene) soft middle block. KRATON G-1650 contains about 30 mass % of polystyrene blocks.

Representative examples of solvents that can be combined with the polymer and active agent include chloroform, acetone, water (buffered saline), dimethylsulfoxide, propylene glycol methyl ether, iso-propylalcohol, n-propylalcohol, methanol, ethanol, tetrahydrofuran, dimethylformamide, dimethylacetamide, benzene, toluene, xylene, hexane, cyclohexane, pentane, heptane, octane, nonane, decane, decalin, ethyl acetate, butyl acetate, isobutyl acetate, isopropyl acetate, butanol, diacetone alcohol, benzyl alcohol, 2-butane, cyclohexanone, dioxane, methylene chloride, carbon tetrachloride, tetrachloroethylene, tetrachloro ethane, chlorobenzene, 1,1,1-trichloroethane, formamide, hexafluoroisopropanol, 1,1,1-trifluoroethanol, and hexamethyl phosphoramide and a combination thereof.

The active agent may be any substance capable of exerting a therapeutic or prophylactic effect in the practice of the present invention. Examples of such active agents include antiproliferative, antineoplastic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, and antioxidant substances as well as combinations thereof. An example of an antiproliferative substance is actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich 1001 West Saint Paul Avenue, Milwaukee, Wis. 53233; or COSMEGEN available from Merck). Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I₁, actinomycin X₁, and actinomycin C₁. Examples of antineoplastics include paclitaxel and docetaxel. Examples of antiplatelets, anticoagulants, antifibrins, and antithrombins include aspirin, sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vaproprost, prostacyclin and prostacyclin analogs, dextran, D-phe-pro-arg-chloromethylketone (synthetic anti-thrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist, recombinant hirudin, thrombin inhibitor (available from Biogen), and 7E-3B® (an antiplatelet drug from Centocor). Examples of antimitotic agents include methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin, and mutamycin. Examples of cytostatic or antiproliferative agents include angiopoietin (a somatostatin analog from Ibsen), angiotensin converting enzyme inhibitors such as CAPTOPRIL (available from Squibb), CILAZAPRIL (available from Hoffman-LaRoche), or LISINOPRIL (available from Merck & Co., Whitehouse Station, N.J.), calcium channel blockers (such as Nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, histamine antagonist, LOVASTATIN (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merck & Co.), monoclonal antibodies (such as PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor (available from Glazo), Seramin (a PDGF antagonist), serotonin blockers, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic substances or agents that may be appropriate include alpha-interferon, genetically engineered epithelial cells, dexamethasone, estradiol, clobetasol propionate, cisplatin, insulin sensitizers, receptor tyrosine kinase inhibitors and carboplatin. Exposure of the composition to the active agent should not adversely alter the active agent's

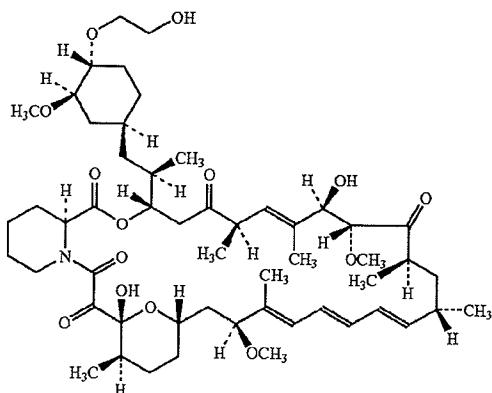
CORD120670

US 7,285,304 B1

19

composition or characteristic. Accordingly, the particular active agent is selected for compatibility with the blended composition.

In one embodiment, rapamycin, or a functional or structural derivative such as 40-O-(2-hydroxy)ethyl-rapamycin can be used. The chemical structure for 40-O-(2-hydroxy)ethyl-rapamycin is as follows:



Analogs or derivatives of 40-O-(2-hydroxy)ethyl-rapamycin can also be used, examples of which include but are not limited to 40-O-(3-hydroxy)propyl-rapamycin and 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin.

40-O-(2-hydroxy)ethyl-rapamycin binds to the cytosolic immunophillin FKBP12 and inhibits growth factor-driven cell proliferation, including that of T-cells and vascular smooth muscle cells. The actions of 40-O-(2-hydroxy)ethyl-rapamycin occur late in the cell cycle (i.e., late G1 stage) compared to other immunosuppressive agents such as tacrolimus or cyclosporine which block transcriptional activation of early T-cell-specific genes. Since 40-O-(2-hydroxy)ethyl-rapamycin can act as a potent anti-proliferative agent, it is believed that 40-O-(2-hydroxy)ethyl-rapamycin can be an effective agent to treat restenosis by being delivered to a local treatment site from a polymeric coated implantable device such as a stent.

The release rate of 40-O-(2-hydroxy)ethyl-rapamycin can be advantageously controlled by various methods and coatings as described herein. In particular, by using the methods and coatings of the present invention, the release rate of the 40-O-(2-hydroxy)ethyl-rapamycin, or analog or derivative thereof, can be less than about 50% in 24 hours.

The 40-O-(2-hydroxy)ethyl-rapamycin, or analog or derivative thereof, in the reservoir layer can be in the amount of about 50 µg to about 500 µg, more narrowly about 90 µg to about 350 µg, and the polymer can be in the amount of about 50 µg to about 1000 µg, more narrowly about 90 µg to about 500 µg. When the 40-O-(2-hydroxy)ethyl-rapamycin is blended with a polymer for the reservoir layer, the ratio of 40-O-(2-hydroxy)ethyl-rapamycin, or analog or derivative thereof, to polymer by weight in the reservoir layer can be about 1:2.8 to about 1.5:1.

The dosage or concentration of the active agent required to produce a therapeutic effect should be less than the level at which the active agent produces unwanted toxic effects and greater than the level at which non-therapeutic results are obtained. The dosage or concentration of the active agent required to inhibit the desired cellular activity of the vas-

20

cular region, for example, can depend upon factors such as the particular circumstances of the patient; the nature of the trauma; the nature of the therapy desired; the time over which the ingredient administered resides at the vascular site; and if other bioactive substances are employed, the nature and type of the substance or combination of substances. Therapeutically effective dosages can be determined empirically, for example by infusing vessels from suitable animal model systems and using immunohistochemical, fluorescent or electron microscopy methods to detect the agent and its effects, or by conducting suitable in vitro studies. Standard pharmacological test procedures to determine dosages are understood by one of ordinary skill in the art.

15 Forming a Barrier Layer to Reduce the Rate of Release

In some coatings, the release rate of the active agent may 20 be too high to be clinically useful. A barrier layer can reduce the rate of release or delay the time at which the active agent is released from the reservoir layer.

In accordance with one embodiment, the barrier layer can be applied on a selected region of the reservoir layer to form 25 a rate reducing member. The barrier layer can be applied to the reservoir layer prior to or subsequent to the fluid treatment. If the barrier layer is applied to the reservoir layer prior to the fluid treatment, the solvent in the barrier layer should be allowed to evaporate to form a dry coating prior 30 to application of the fluid. Similarly, if the barrier layer is applied to the reservoir layer subsequent to the fluid treatment, the barrier layer should be applied after the fluid has been allowed to evaporate from the coating.

The composition for the barrier layer can be substantially 35 free of active agents. Alternatively, for maximum blood compatibility, compounds such as polyethylene glycol, heparin, heparin derivatives having hydrophobic counterions, or polyethylene oxide can be added to the barrier layer, or disposed on top of the barrier layer.

40 The choice of polymer for the barrier layer can be the same as the selected polymer for the reservoir. The use of the same polymer, as described for some of the embodiments, significantly reduces or eliminates any interfacial incompatibilities, such as lack of adhesion, which may exist in the 45 employment of two different polymeric layers.

Polymers that can be used for a barrier layer include the examples of polymers listed above for the reservoir layer. Representative examples of polymers for the barrier layer also include polytetrafluoroethylene, perfluoro elastomers, 50 ethylene-tetrafluoroethylene copolymer, fluoroethylene-alkyl vinyl ether copolymer, polyhexafluoropropylene, low density linear polyethylenes having high molecular weights, ethylene-olefin copolymers, atactic polypropylene, polyisobutene, polybutenes, polybutenes, styrene-ethylene-styrene block copolymers, styrene-butadiene-styrene block copolymers, and ethylene methacrylic acid copolymers of low methacrylic acid content.

EVAL is functionally a very suitable choice of polymer 60 for the barrier layer. The copolymer can comprise a mole percent of ethylene of from about 27% to about 48%. Fluoropolymers are also a suitable choice for the barrier layer composition. For example, polyvinylidene fluoride (otherwise known as KYNAR, available from ATOFINA 65 Chemicals, Philadelphia, Pa.) can be dissolved in acetone, methylethylketone, dimethylacetamide, and cyclohexanone, and can optionally be combined with EVAL to form the

CORD120671

US 7,285,304 B1

21

barrier layer composition. Also, solution processing of fluoropolymers is possible, particularly the low crystallinity varieties such as CYTOP available from Asahi Glass and TEFLON AF available from DuPont. Solutions of up to about 15% (w/w) are possible in perfluoro solvents, such as FC-75 (available from 3M under the brand name FLUORINERT), which are non-polar, low boiling solvents. Such volatility allows the solvent to be easily and quickly evaporated following the application of the polymer-solvent solution to the implantable device.

PBMA and ethylene-vinyl acetate copolymers can also be especially suitable polymers for the barrier layer. PBMA, for example, can be dissolved in a solution of xylene, acetone and HFE FLUX REMOVER (Techspray, Amarillo, Tex.). In another embodiment, the polymer in the barrier layer is PBMA or a mixture of PBMA and an ethylene-vinyl acetate copolymer.

Other choices of polymers for the rate-limiting membrane include, but are not limited to, ethylene-anhydride copolymers; and ethylene-acrylic acid copolymers having, for example, a mole % of acrylic acid from about 2% to about 25%. The ethylene-anhydride copolymer available from Bynel adheres well to EVAL and thus would function well as a barrier layer over a reservoir layer made from EVAL. The copolymer can be dissolved in organic solvents, such as dimethylsulfoxide and dimethylacetamide. Ethylene vinyl acetate polymers can be dissolved in organic solvents, such as toluene and n-butyl acetate. Ethylene-acrylic acid copolymers can be dissolved in organic solvents, such as methanol, isopropyl alcohol, and dimethylsulfoxide.

Yet another choice of polymer for the rate-limiting membrane is a cross-linked silicone elastomer. Loose silicone and silicone with very low cross-linking are thought to cause an inflammatory biological response. However, it is believed that a thoroughly cross-linked silicone elastomer, having low levels of leachable silicone polymer and oligomer, is an essentially non-inflammatory substance. Silicone elastomers, such as Nusil MED-4750, MED-4755, or MED2-6640, having high tensile strengths, for example between 1200 psi and 1500 psi, will likely have the best durability during crimping, delivery, and expansion of a stent as well as good adhesion to a reservoir layer, e.g., EVAL or the surface of an implantable device.

The composition for a rate-reducing membrane or diffusion barrier layer can be prepared by the methods used to prepare a polymer solution as described above. The polymer can comprise from about 0.1% to about 35%, more narrowly from about 1% to about 20% by weight of the total weight of the composition, and the solvent can comprise from about 65% to about 99.9%, more narrowly from about 80% to about 98% by weight of the total weight of the composition. Selection of a specific weight ratio of the polymer and solvent is dependent on factors such as, but not limited to, the type of polymer and solvent employed, the type of underlying reservoir layer, and the method of application.

Forming a Primer Layer

The presence of an active agent in a polymeric matrix can interfere with the ability of the matrix to adhere effectively to the surface of the device. Increasing the quantity of the active agent reduces the effectiveness of the adhesion. High drug loadings in the coating can hinder the retention of the coating on the surface of the device. A primer layer can serve as a functionally useful intermediary layer between the surface of the device and an active agent-containing or reservoir coating. The primer layer provides an adhesive tie

22

between the reservoir coating and the device—which, in effect, would also allow for the quantity of the active agent in the reservoir coating to be increased without compromising the ability of the reservoir coating to be effectively contained on the device during delivery and, if applicable, expansion of the device.

The primer composition can be prepared by adding a predetermined amount of a polymer to a predetermined amount of a compatible solvent. By way of example, and not limitation, the polymer can comprise from about 0.1% to about 35%, more narrowly from about 1% to about 20% by weight of the total weight of the composition, and the solvent can comprise from about 65% to about 99.9%, more narrowly from about 80% to about 98% by weight of the total weight of the primer composition. A specific weight ratio is dependent on factors such as the material from which the implantable device is made, the geometrical structure of the device, the choice of polymer-solvent combination, and the method of application.

Representative examples of polymers for the primer layer include, but are not limited to, polyisocyanates, such as triisocyanurate and polyisocyanate; polyethers; polyurethanes based on diphenylmethane diisocyanate; acrylates, such as copolymers of ethyl acrylate and methacrylic acid; titanates, such as tetra-iso-propyl titanate and tetra-n-butyl titanate; zirconates, such as n-propyl zirconate and n-butyl zirconate; silane coupling agents, such as 3-aminopropyltriethoxysilane and (3-glycidoxypropyl) methyltriethoxysilane; high amine content polymers, such as polyethylene-amine, polyallylamine, and polylysine; polymers with a high content of hydrogen bonding groups, such as polyethylene-co-polyvinyl alcohol, ethylene vinyl acetate, and melamine formaldehydes; and unsaturated polymers and prepolymers, such as polycaprolactone diacrylates, polyacrylates with at least two acrylate groups, and polyacrylated polyurethanes. With the use of unsaturated prepolymers, a free radical or UV initiator can be added to the composition for the thermal or UV curing or cross-linking process, as is understood by one of ordinary skill in the art.

Representative examples of polymers that can be used for the primer material also include those polymers that can be used for the reservoir layer as described above. The use of the same polymer significantly reduces or eliminates any interfacial incompatibilities, such as lack of an adhesive tie or bond, which may exist with the employment of two different polymeric layers.

EVAL is a very suitable choice of polymer for the primer layer. The copolymer possesses good adhesive qualities to the surface of a stent, particularly stainless steel surfaces, and has illustrated the ability to expand with a stent without any significant detachment of the copolymer from the surface of the stent. The copolymer can comprise a mole percent of ethylene of from about 27% to about 48%.

Methods For Applying the Compositions to the Device

Application of the composition can be by any conventional method, such as by spraying the composition onto the prosthesis or by immersing the prosthesis in the composition. Operations such as wiping, centrifugation, blowing, or other web-clearing acts can also be performed to achieve a more uniform coating. Briefly, wiping refers to physical removal of excess coating from the surface of the stent; centrifugation refers to rapid rotation of the stent about an axis of rotation; and blowing refers to application of air at a

CORD120672

US 7,285,304 B1

23

selected pressure to the deposited coating. Any excess coating can also be vacuumed off the surface of the device.

If the optional primer layer is to be formed on the device, the primer composition can first be applied to a designated region of the surface of the device. The solvent(s) is removed from the composition by allowing the solvent(s) to evaporate. The evaporation can be induced by heating the device at a predetermined temperature for a predetermined period of time. For example, the device can be heated at a temperature of about 60° C. for about 10 minutes to about 24 hours. The heating can be conducted in an anhydrous atmosphere and at ambient pressure and should not exceed the temperature which would adversely affect the active agent. The heating can also be conducted under a vacuum condition.

The composition containing the active agent can be applied to a designated region of the surface of the device. If the optional primer layer has been formed on the surface of the device, active agent-containing composition can be applied to the dry primer layer. Thereafter, the solvent(s) can be removed from the reservoir layer as described above for the primer layer.

Examples of the Device

Examples of implantable devices for the present invention include self-expandable stents, balloon-expandable stents, stent-grafts, grafts (e.g., aortic grafts), artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation, Santa Clara, Calif.). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY), stainless steel (316L), high nitrogen stainless steel, e.g., BIODUR 108, cobalt chrome alloy L-605, "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co., Jenkintown, Pa. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention.

The embodiments of the present invention may be particularly useful for the coatings of small vessel stents. Small vessels stents can be generally categorized as having inner diameters of less than 2.5 mm in an expanded state. Because of their small size, small vessel stents offer unique challenges for drug delivery. In particular, as compared to conventionally sized stents, small vessel stents have a greater surface:volume ratio. Therefore, when a small vessel stent is inserted into a biological lumen, the vessel tissue surrounding a small vessel stent is exposed to a greater concentration of polymer. The present invention can be used to reduce the amount of polymer that is needed on the stent structure and still maintain an efficacious release rate. The present invention, therefore, can reduce the risk of an inflammatory response by the vessel tissue when small stents are used as a drug delivery device in small vessels.

24

Method of Use

In accordance with the above-described method, the active agent can be applied to a device, e.g., a stent, retained on the device during delivery and released at a desired control rate and for a predetermined duration of time at the site of implantation. A stent having the above-described coating layers is useful for a variety of medical procedures, including, by way of example, treatment of obstructions caused by tumors in bile ducts, esophagus, trachea/bronchi and other biological passageways. A stent having the above-described coating layers is particularly useful for treating occluded regions of blood vessels caused by abnormal or inappropriate migration and proliferation of smooth muscle cells, thrombosis, and restenosis. Stents may be placed in a wide array of blood vessels, both arteries and veins. Representative examples of sites include the iliac, renal, and coronary arteries.

Briefly, an angiogram is first performed to determine the appropriate positioning for stent therapy. Angiography is typically accomplished by injecting a radiopaque contrasting agent through a catheter inserted into an artery or vein as an x-ray is taken. A guidewire is then advanced through the lesion or proposed site of treatment. Over the guidewire is passed a delivery catheter, which allows a stent in its collapsed configuration to be inserted into the passageway. The delivery catheter is inserted either percutaneously, or by surgery, into the femoral artery, brachial artery, femoral vein, or brachial vein, and advanced into the appropriate blood vessel by steering the catheter through the vascular system under fluoroscopic guidance. A stent having the above-described coating layers may then be expanded at the desired area of treatment. A post insertion angiogram may also be utilized to confirm appropriate positioning.

EXAMPLES

The embodiments of the invention will be illustrated by the following set forth examples which are being given by way of illustration only and not by way of limitation. All parameters and data are not be construed to unduly limit the scope of the embodiments of the invention.

Example 1

18 mm VISION stents (available from Guidant Corporation) were coated by spraying a 2% (w/w) solution of polybutylmethacrylate ("PBMA") mixed with a solvent having 60% acetone and 40% xylene (w/w). The solvent was removed by baking at 80° C. for 30 minutes. The target primer weight was 160 µg. A solution of 2% (w/w) PBMA and 40-O-(2-hydroxy)ethyl-rapamycin in a mixture of 60% acetone and 40% xylene (w/w) was spray coated onto the stents. The drug to polymer ratio for the coating was 1.25 to 1, with a target reservoir coating weight of 288 µg. The target drug loading was 160 µg. The stents were then baked at 50° C. for 2 hours to produce dry coatings.

Example 2

The stents were separated into two test groups. Group A served as the control group, and Group B was exposed to a fluid treatment. In particular, the stents of Group B were sprayed with a solution of pure ethanol for five spray cycles. In particular, the following Table 4 lists the spray process parameters that were used to conduct the fluid treatment process:

CORD120673

A1346

US 7,285,304 B1

25

TABLE 4

Parameter	Set Value	Units
<u>Spray Head</u>		
Spray nozzle temperature	26 ± 2	° C.
Aerosolization pressure (non-activated)	15 ± 2.5	psi
Distance from spray nozzle to coating mandrel pin	10-12	mm
Solution barrel pressure	2.5	psi
Needle valve lift pressure	80 ± 10	psi
<u>Heat Nozzle</u>		
Temperature	26 ± 2	° C.
Air Pressure	12-15	psi
Distance from heat nozzle to coating mandrel pin	10-15	mm

The stents of Group B were then baked to essentially remove the ethanol.

Example 3

The drug-coated stents were placed on stent holders of a Vankel Bio-Dis release rate tester (Vankel, Inc., Cary, N.C.). 25 3 stents from each test group were dipped into an artificial medium for about 1 hour to extract the 40-O-(2-hydroxy) ethyl-rapamycin from the stent coatings. The artificial medium included a phosphate buffer saline solution (10 mM, pH 7.4) and 1% TRITON X-100 (Sigma Corporation) which stabilizes the 40-O-(2-hydroxy)ethyl-rapamycin in the testing solution. Each stent was tested in a separate testing solution to prevent cross-contamination. After extraction, each of the solutions was separately analyzed for the amount of drug released from the stent coatings by using an HPLC process. The HPLC system consisted of a Waters 2690 system. After the drug solutions were analyzed by HPLC, the results were quantified by comparing the release rate results with a reference standard.

Each of the stents were then dipped in fresh extraction solutions for another 6 hours (7 hours total). The solutions were analyzed by HPLC as described above. Finally, the stents were dipped in fresh extraction solutions for another 17 hours (24 hours total). The solutions were again analyzed by HPLC as described above.

Next, the total drug content of the coatings was determined. First, 3 stents from each test group were placed in volumetric flasks. Each stent was placed in a separate flask. An appropriate amount of the extraction solvent acetonitrile with 0.02% butylated hydroxytoluene as a protectant was added to each flask. The flasks were sonicated for a sufficient time to extract all of the drug from the reservoir regions. Then, the solution in the flasks was filled to mark with the solvent solution. The drug solutions for each stent were separately analyzed by HPLC. The HPLC release rate results were quantified by comparing the results with a reference standard. The total drug content of the stents was then calculated.

The drug release profile could then be generated by plotting cumulative drug released in the medium vs. time. The percentage of drug released at a specific time was determined by comparing the cumulative drug released with the total content data. The results demonstrate that the fluid treatment process substantially reduces the release rate of the active agent. The results for the total content analysis are

26

summarized in Table 5, the drug release profile is summarized in Table 6, and the release rate for each test group is summarized in Table 7.

5

TABLE 5

10	Group A			Group B		
	Stent 1	Stent 2	Stent 3	Stent 1	Stent 2	Stent 3
Theoretical Total Recovery (μg)	149.4	174.4	166.1	165.0	163.3	166.1
Total Recovered (μg)	142.4	161.6	150.7	128.2	135.0	133.1
% Recovered	95	93	91	78	83	80

20

TABLE 6

25	Group A (μg released)			Group B (μg released)		
	Stent 1	Stent 2	Stent 3	Stent 1	Stent 2	Stent 3
Time (hours)						
1	34.93	30.37	36.89	7.82	3.67	1.88
7	55.44	54.30	62.03	25.50	9.92	5.31
24	74.55	82.69	89.62	46.40	16.84	10.14
Average for Group (24 hours)	82.29			24.46		
30 Standard Deviation for Group		7.54			19.29	

35

TABLE 7

40	Group A (% of drug released)			Group B (% of drug released)		
	Stent 1	Stent 2	Stent 3	Stent 1	Stent 2	Stent 3
Time (hours)						
1	25	19	24	5	2	1
7	39	34	41	17	7	4
24	52	51	59	31	11	7
Average for Group (24 hours)	54.35			16.24		
45 Standard Deviation for Group		4.49			12.80	

50

Example 4

55 The following experiment was conducted in order to obtain information on how the fluid treatment process could affect polymer morphology. Pellets of poly(vinylidene fluoride-co-hexafluoropropene) (SOLEX 21508, available from Solvay Solexis PVDF, Thorofare, N.J.) were placed in a 60 sealable container. The treatment fluid, ethyl acetate, was added to the container at a 1:7 polymer:fluid ratio (w/w) and the container was sealed. The contents of the container were agitated at room temperature for about five hours by using a magnetic stir bar. Upon visible inspection, the pellets about doubled in size, indicating that the fluid caused the polymer to swell. After the treatment, the polymer pellets were removed from the container and dried at 50° C. overnight.

CORD120674

US 7,285,304 B1

27

A Fourier Transform Infrared (FTIR) analysis was conducted on a control group (i.e., pellets of poly(vinylidene fluoride-co-hexafluoropropene) which had not been exposed to the fluid treatment). The results for the control group are illustrated in the spectrograph of FIG. 5A. An FTIR analysis was also conducted on the pellets exposed to the fluid treatment. The results for the fluid treatment group are illustrated in the spectrograph of FIG. 5B. The spectra of FIGS. 5A and 5B are substantially similar, except that a peak near 975 cm⁻¹ appears for the polymer treated with the fluid as shown in FIG. 5B.

It was confirmed by conducting a differential scanning calorimetry (DSC) experiment that the peak near 975 cm⁻¹ indicated an increase in percent crystallinity for the polymer. In particular, it was determined that the polymer treated with the fluid had a melting enthalpy of about 35 J/gram, whereas a control sample of polymer that was untreated had a melting enthalpy of about 24 J/gram. The increased melting enthalpy of the treated polymer indicated an increase in percent crystallinity.

Example 5

18 mm VISION stents (available from Guidant Corporation) are coated by spraying a 2% (w/w) solution of poly (vinylidene fluoride-co-hexafluoropropene) (e.g., SOLEF 21508) and 40-O-(2-hydroxy)ethyl-rapamycin mixed with a solvent having 30:70 acetone/cyclohexanone (w/w). The drug to polymer ratio for the coating is 1.25 to 1. The target drug loading is 160 µg. The solvent is removed by baking at 50° C. for 2 hours to produce a dry drug coating. Next, the stents are immersed in a hydrofluoroether solvent (e.g., NOVEC HFE7200, ethoxynonafluorobutane (C₄F₉OC₂H₅), available from 3M, St. Paul, Minn.) for five minutes for a fluid treatment. The stents are then removed from the hydrofluoroether solvent and baked to remove essentially all of the fluid.

Example 6

18 mm VISION stents (available from Guidant Corporation) are coated by spraying a 2% (w/w) solution of PBMA mixed with a solvent having 60% acetone and 40% xylene (w/w). The solvent is removed by baking at 80° C. for 30 minutes. The target primer weight is 160 µg. A solution of 2% (w/w) PBMA and 40-O-(2-hydroxy)ethyl-rapamycin in a mixture of 60% acetone and 40% xylene (w/w) is spray coated onto the stents. The drug to polymer ratio for the coating is 1.25 to 1, with a target reservoir coating weight of about 288 µg. The target drug loading is 160 µg. The stents are then baked at 50° C. for 2 hours to produce dry coatings. Next, the stents are sprayed with acetone for five spray cycles. The acetone is allowed to evaporate to remove essentially all of the fluid from the coatings.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

What is claimed is:

1. A method of manufacturing a drug delivery implantable medical device, comprising:
applying a composition to an implantable medical device, the composition including a polymer, an active agent and a solvent;

28

allowing the solvent to evaporate to form a dry coating, the dry coating comprising less than about 2% residual fluid content (w/w);

applying a fluid to the dry coating, the fluid being substantially or completely free from any polymer; and removing the fluid from the coating.

2. The method of claim 1, wherein fluid is substantially or completely free from any active agents.

3. The method of claim 1, wherein the active agent is at least partially soluble in the fluid.

4. The method of claim 1, additionally comprising prior to applying the composition, forming a primer layer on a surface of the implantable medical device.

5. The method of claim 1, additionally comprising forming a barrier layer on the dry coating wherein the application of the fluid is performed prior to forming the barrier layer.

6. The method of claim 1, wherein the device is a stent.

7. The method of claim 1, wherein the polymer comprises an ethylene vinyl alcohol copolymer, an ethylene-vinyl acetate copolymer, poly(vinylidene fluoride-co-hexafluoropropene), poly(butylmethacrylate), or a combination of the same.

8. The method of claim 1, wherein the dry coating comprises less than about 1% residual fluid content (w/w).

9. The method of claim 1, wherein the active agent is rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin, paclitaxel, docetaxel, or a functional analog or structural derivative thereof.

10. The method of claim 1, wherein subsequent to the act of applying the fluid the total content of the active agent in the coating is at least 80% of the total content of the active agent in the coating prior to application of the fluid.

11. The method of claim 1, wherein the duration of exposure of the fluid is sufficient to decrease the release rate of the active agent from the coating after the coating has been implanted into a biological lumen.

12. The method of claim 1, wherein applying the fluid includes spraying the fluid onto the coating or immersing the device into a bath of fluid.

13. The method of claim 12, wherein the device is immersed for about 30 minutes to about twelve hours.

14. The method of claim 1, wherein the fluid is selected from the group consisting of chloroform, acetone, water, dimethylsulfoxide, propylene glycol methyl ether, iso-propylalcohol, n-propylalcohol, methanol, ethanol, tetrahydrofuran, dimethylformamide, dimethylacetamide, benzene, toluene, xylene, hexane, cyclohexane, pentane, heptane, octane, nonane, decane, decalin, ethyl acetate, butyl acetate, isobutyl acetate, isopropyl acetate, butanol, diacetone alcohol, benzyl alcohol, 2-butanone, cyclohexanone, dioxane, methylene chloride, carbon tetrachloride, tetrachloroethylene, tetrachloroethane, chlorobenzene, 1,1,1-trichloroethane, formamide, hexafluoroisopropanol, 1,1,1-trifluoroethanol, acetonitrile, hexamethyl phosphoramide and a combination thereof.

15. The method of claim 1, wherein the fluid is only applied to a portion of the device along the length of the device.

16. The method of claim 1, wherein the solvent and the fluid are different.

17. The method of claim 1, wherein subsequent to the removal of the fluid, the release rate of the active agent is less than about 30% in 24 hours.

18. The method of claim 1, wherein the temperature of the fluid is greater than room temperature.

CORD120675

US 7,285,304 B1

29

19. The method of claim 1, wherein the temperature of the fluid is equal to or greater than the glass transition temperature of the polymer.

20. The method of claim 1, wherein the application of the fluid to the dry coating causes the percent crystallinity of the polymer in the coating to increase.

21. The method of claim 1, wherein the polymer is a blend of two or more polymers.

22. The method of claim 1, wherein the polymer is a semicrystalline polymer having about 10 to 75 percent crystallinity prior to the application of the fluid.

23. The method of claim 1, wherein the polymer is a block copolymer or a graft copolymer.

24. The method of claim 1, wherein the polymer exhibits two or more glass transition temperatures, and wherein the temperature of the fluid is equal to or greater than the lowest exhibited glass transition temperature of the polymer.

25. The method of claim 1, wherein the polymer exhibits two or more glass transition temperatures, and wherein the temperature of the fluid is equal to or greater than the highest exhibited glass transition temperature of the polymer.

26. A method of manufacturing a stent coating, comprising:

applying a composition to a stent, the composition including a semicrystalline polymer and a solvent; allowing the solvent to evaporate to form a dry coating, the dry coating comprising less than about 2% residual fluid content (w/w); and exposing the coating to a fluid for a sufficient duration to increase the crystallinity of the polymer in at least a portion of the coating, the fluid being substantially or completely free from any polymer; and removing the fluid from the coating.

27. The method of claim 26, wherein the polymer has about 10 to 75 percent crystallinity prior to the act of exposing.

28. The method of claim 26, wherein the polymer comprises an ethylene vinyl alcohol copolymer or poly(vinylidene fluoride-co-hexafluoropropene).

29. The method of claim 26, wherein the dry coating comprises less than about 1% residual fluid content (w/w).

30

30. The method of claim 26, wherein exposing the coating to a fluid includes immersing the stent into a bath of fluid.

31. The method of claim 30, wherein the stent is immersed for about 30 minutes to about twelve hours.

32. The method of claim 1, wherein the polymer comprises a polyvinyl aromatic polymer.

33. The method of claim 26, wherein the polymer comprises a polyvinyl aromatic polymer.

34. The method of claim 26 wherein the composition further comprises an active agent.

35. The method of claim 1, wherein the fluid is completely free from any polymer.

36. The method of claim 1, wherein the fluid is completely free from any polymer and is substantially or completely free from the active agent.

37. The method of claim 1, wherein the fluid is completely free from any polymer and is completely free from the active agent.

38. The method of claim 1, wherein the fluid is completely free from the active agent.

39. The method of claim 1, wherein the fluid is substantially free from the active agent.

40. The method of claim 26, wherein the fluid is completely free from any polymer.

41. The method of claim 26, wherein the fluid is substantially free from an active agent.

42. The method of claim 26, wherein the fluid is completely free from an active agent.

43. The method of claim 1, wherein the composition forms a reservoir layer and wherein the dry coating includes a barrier layer formed over the reservoir layer prior to application of the fluid.

44. The method of claim 1, wherein the fluid is removed by evaporation.

45. The method of claim 26, wherein the fluid is removed by evaporation.

46. The method of claim 26, wherein the fluid is completely free of any polymer and is completely free from an active agent.

* * * * *

CORD120676

A1349



US007300662B2

(12) **United States Patent**
Falotico et al.

(10) **Patent No.:** US 7,300,662 B2
(45) **Date of Patent:** *Nov. 27, 2007

(54) **DRUG/DRUG DELIVERY SYSTEMS FOR THE PREVENTION AND TREATMENT OF VASCULAR DISEASE**

(75) Inventors: **Robert Falotico**, Belle Mead, NJ (US); **Gregory A. Kopia**, Hillsborough, NJ (US); **Gerard H. Llanos**, Stewartsville, NJ (US)

(73) Assignee: **Cordis Corporation**, Miami Lakes, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 503 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: 10/829,074

(22) Filed: Apr. 21, 2004

(65) **Prior Publication Data**

US 2004/0260268 A1 Dec. 23, 2004

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/850,293, filed on May 7, 2001, now abandoned, which is a continuation-in-part of application No. 09/575,480, filed on May 19, 2000.

(60) Provisional application No. 60/263,979, filed on Jan. 25, 2001, provisional application No. 60/263,806, filed on Jan. 24, 2001, provisional application No. 60/262,614, filed on Jan. 18, 2001, provisional application No. 60/262,461, filed on Jan. 18, 2001, provisional application No. 60/204,417, filed on May 12, 2000.

(51) **Int. Cl.**
A61F 2/00 (2006.01)
A61F 2/06 (2006.01)

(52) **U.S. Cl.** 424/424; 623/1.42; 623/1.45

(58) **Field of Classification Search** 424/422-426; 623/1.42-1.48
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

861,659 A	7/1907	Johnston	464/147
3,051,677 A	8/1962	Rexford	522/156
3,279,996 A	10/1966	Long et al.	424/424
3,526,005 A	9/1970	Bokros	623/11.11
3,599,641 A	8/1971	Sheridan	604/256

(Continued)

FOREIGN PATENT DOCUMENTS

DE 3205942 A1 9/1983

(Continued)

OTHER PUBLICATIONS

Boston Scientific, "Measuring DES Efficacy," www.taxus-stent.com/usa/efficacy.html, pp. 1-3, copyright 2006.*

(Continued)

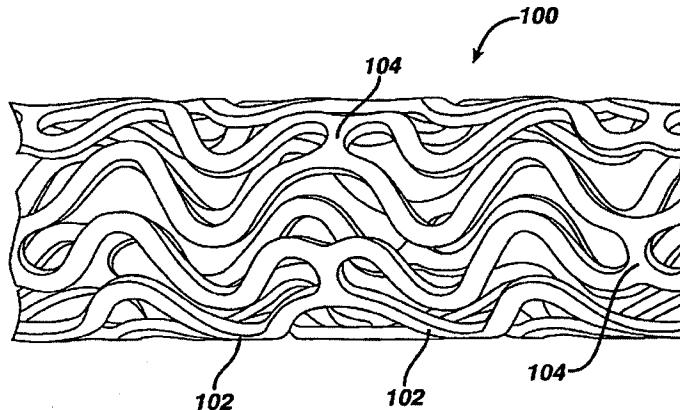
Primary Examiner—Sharon E. Kennedy

(74) *Attorney, Agent, or Firm*—Woodcock Washburn LLP

(57) **ABSTRACT**

A drug and drug delivery system may be utilized in the treatment of vascular disease. A local delivery system is coated with rapamycin or other suitable drug, agent or compound and delivered intraluminally for the treatment and prevention of neointimal hyperplasia following percutaneous transluminal coronary angiography. The local delivery of the drugs or agents provides for increased effectiveness and lower systemic toxicity.

25 Claims, 2 Drawing Sheets



US 7,300,662 B2

Page 2

U.S. PATENT DOCUMENTS					
3,657,744 A	4/1972 Ersek	5,047,020 A	9/1991 Hsu	604/266
3,744,596 A	7/1973 Sander	5,049,132 A	9/1991 Shaffer et al.		
3,779,805 A	12/1973 Alsberg	5,053,048 A	9/1991 Larm et al.	427/2.1
3,929,992 A	12/1975 Sehgal et al.	5,059,166 A	10/1991 Pinchuk		
3,932,627 A	1/1976 Margraf	5,061,275 A	10/1991 Fischell et al.	600/3
3,948,254 A	4/1976 Zaffaroni	5,061,750 A	10/1991 Wallsten et al.		
3,952,334 A	4/1976 Bokros et al.	5,064,435 A	11/1991 Feijen et al.		
3,968,800 A	7/1976 Vilasi	5,092,877 A	3/1992 Porter		
4,069,307 A	1/1978 Higuchi et al.	5,102,417 A	3/1992 Pinchuk		
4,076,285 A	2/1978 Martinez	5,104,404 A	4/1992 Palmaz		
4,292,965 A	10/1981 Nash et al.	5,116,365 A	4/1992 Wolff		
4,299,226 A	11/1981 Banka	5,122,154 A	5/1992 Hillstead		
4,300,244 A	11/1981 Bokros	5,131,908 A	6/1992 Rhodes		
4,312,920 A	1/1982 Pierce et al.	5,133,732 A	7/1992 Dardik et al.		
4,321,711 A	3/1982 Mano	5,134,192 A	7/1992 Wiktor		
4,323,071 A	4/1982 Simpson et al.	5,135,536 A	7/1992 Feijen et al.		
4,390,599 A	6/1983 Broyles	5,163,952 A	8/1992 Froix		
4,413,359 A	11/1983 Akiyama et al.	5,163,958 A	11/1992 Pinchuk		
4,423,183 A	12/1983 Close	5,171,217 A	12/1992 March et al.	604/507
4,441,216 A	4/1984 Ionescu et al.	5,171,262 A	12/1992 MacGregor		
4,503,569 A	3/1985 Dotter	5,176,660 A	1/1993 Cottenceau et al.		
4,512,338 A	4/1985 Balko et al.	5,176,972 A	1/1993 Truckai		
4,550,447 A	11/1985 Seiler, Jr. et al.	5,178,618 A	1/1993 Bloom et al.	430/14
4,553,545 A	11/1985 Maass et al.	5,180,366 A	1/1993 Kandarpa		
4,560,374 A	12/1985 Hammerslag	5,182,317 A	1/1993 Woods		
4,562,596 A	1/1986 Kronberg	5,185,408 A	1/1993 Winters et al.		
4,565,740 A	1/1986 Golander et al.	5,192,307 A	2/1993 Tang et al.		
4,580,568 A	4/1986 Gianturco	5,195,984 A	3/1993 Froix		
4,613,665 A	9/1986 Larm	5,202,332 A	3/1993 Hughes et al.	514/291
4,642,111 A	2/1987 Sakamoto et al.	5,213,576 A	5/1993 Abuso et al.		
4,655,771 A	4/1987 Wallsten	5,213,898 A	5/1993 Larm et al.	428/422
4,656,083 A	4/1987 Hoffman et al.	5,217,483 A	6/1993 Tower		
4,676,241 A	6/1987 Webb et al.	5,222,971 A	6/1993 Willard et al.		
4,678,466 A	7/1987 Rosenwald	5,226,913 A	7/1993 Pinchuk		
4,687,482 A	8/1987 Hanson	5,234,456 A	8/1993 Silvestrini		
4,689,046 A	8/1987 Bokros	5,246,445 A	9/1993 Yachia et al.		
4,731,054 A	3/1988 Billeter et al.	5,258,020 A	11/1993 Froix		
4,733,665 A	3/1988 Palmaz	5,258,021 A	11/1993 Duran		
4,739,762 A	4/1988 Palmaz	5,262,451 A	11/1993 Winters et al.		
4,740,207 A	4/1988 Kreamer	5,266,073 A	11/1993 Wall		
4,749,585 A	6/1988 Greco et al.	5,272,012 A	12/1993 Opolski	428/423.1
4,753,652 A	6/1988 Langer et al.	5,273,665 A	1/1994 Palmaz	606/108
4,760,849 A	8/1988 Kropf	5,275,622 A	1/1994 Lazarus et al.		
4,768,507 A	9/1988 Fischell et al.	5,282,823 A	2/1994 Schwartz et al.		
4,776,337 A	10/1988 Palmaz	5,282,824 A	2/1994 Gianturco		
4,786,500 A	11/1988 Wong	5,283,257 A	2/1994 Gregory et al.		
4,787,899 A	11/1988 Lazarus	5,288,711 A	2/1994 Mitchell et al.		
4,800,882 A	1/1989 Gianturco	5,290,305 A	3/1994 Inoue		
4,810,784 A	3/1989 Larm	5,292,331 A	3/1994 Boneau		
4,856,516 A	8/1989 Hillstead	5,292,802 A	3/1994 Rhee et al.		
4,871,357 A	10/1989 Hsu et al.	5,304,121 A	4/1994 Sahatjian		
4,872,867 A	10/1989 Joh	5,304,200 A	4/1994 Spaulding		
4,876,109 A	10/1989 Mayer et al.	5,306,250 A	4/1994 March et al.		
4,886,062 A	12/1989 Wiktor	5,308,862 A	5/1994 Ohlstein		
4,907,336 A	3/1990 Gianturco	5,308,889 A	5/1994 Rhee et al.		
4,916,193 A	4/1990 Tang et al.	5,314,444 A	5/1994 Gianturco		
4,954,126 A	9/1990 Wallsten	5,314,472 A	5/1994 Fontaine		
4,969,458 A	11/1990 Wiktor	5,328,471 A	7/1994 Slepian		
4,990,131 A	2/1991 Dardik	5,334,301 A	8/1994 Heinke et al.		
4,990,155 A	2/1991 Wilkoff	5,336,518 A	8/1994 Pallassana et al.		
4,994,071 A	2/1991 MacGregor	5,338,770 A	8/1994 Winters et al.		
4,994,298 A	2/1991 Yasuda	5,342,348 A	8/1994 Kaplan		
4,998,923 A	3/1991 Samson et al.	5,342,387 A	8/1994 Summers		
5,015,253 A	5/1991 MacGregor	5,342,621 A	8/1994 Eury		
5,019,090 A	5/1991 Pinchuk	5,354,257 A	10/1994 Roubin et al.		
5,019,096 A	5/1991 Fox, Jr. et al.	5,354,308 A	10/1994 Simon et al.		
5,029,877 A	7/1991 Fedeli et al.	5,356,433 A	10/1994 Rowland et al.		
5,034,265 A	7/1991 Hoffman et al.	5,366,504 A	11/1994 Andersen et al.		
5,035,706 A	7/1991 Gianturco	5,368,566 A	11/1994 Crocker		
5,041,100 A	8/1991 Rowland et al.	5,370,683 A	12/1994 Fontaine		
5,041,126 A	8/1991 Gianturco	5,370,691 A	12/1994 Samson		
		5,375,612 A	12/1994 Cottenceau et al.		

US 7,300,662 B2

Page 3

5,376,112 A	12/1994	Duran	5,591,224 A	1/1997	Schwartz et al.
5,378,475 A	1/1995	Smith et al. 424/473	5,591,227 A	1/1997	Dinh et al.
5,380,299 A	1/1995	Fearnott et al.	5,599,352 A	2/1997	Dinh et al.
5,382,261 A	1/1995	Palma	5,603,722 A	2/1997	Phan et al.
5,383,853 A	1/1995	Jung et al. 604/103.04	5,604,283 A	2/1997	Wada et al. 524/236
5,383,928 A	1/1995	Scott et al.	5,605,696 A	2/1997	Eury et al.
5,387,235 A	2/1995	Chuter	5,607,463 A	3/1997	Schwartz et al.
5,389,106 A	2/1995	Tower	5,607,475 A	3/1997	Cahalan et al.
5,391,730 A	2/1995	Skotnicki et al. 540/456	5,609,629 A	3/1997	Fearnott et al.
5,393,772 A	2/1995	Yue et al.	5,616,608 A	4/1997	Kinsella et al. 514/449
5,395,390 A	3/1995	Simon et al.	5,620,984 A	4/1997	Bianco et al.
5,397,355 A	3/1995	Marin et al.	5,621,102 A	4/1997	Bianco et al.
5,399,352 A	3/1995	Hanson 424/423	5,622,975 A	4/1997	Singh et al.
5,403,341 A	4/1995	Solar	5,624,411 A	4/1997	Tuch
5,405,377 A	4/1995	Cragg	5,628,785 A	5/1997	Schwartz et al.
5,409,696 A	4/1995	Narayanan et al.	5,629,077 A	5/1997	Turnlund et al.
5,411,549 A	5/1995	Peters	5,629,315 A	5/1997	Bianco et al.
5,415,619 A	5/1995	Lee et al.	5,632,763 A	5/1997	Glastra
5,417,969 A	5/1995	Hsu et al. 424/78.27	5,632,771 A	5/1997	Boatman et al. 623/1.15
5,419,760 A	5/1995	Narciso, Jr.	5,632,776 A	5/1997	Kurumatai et al. 424/423
D359,802 S	6/1995	Fontaine	5,632,840 A	5/1997	Campbell
5,421,955 A	6/1995	Lau	5,635,201 A	6/1997	Fabo 424/443
5,423,885 A	6/1995	Williams	5,637,113 A	6/1997	Tartaglia et al.
5,429,618 A	7/1995	Keogh	5,643,312 A	7/1997	Fischell et al.
5,429,634 A	7/1995	Narciso	5,643,939 A	7/1997	Ohlstein
5,439,446 A	8/1995	Barry	5,646,160 A	7/1997	Morris et al.
5,441,515 A	8/1995	Khosravi et al.	5,648,357 A	7/1997	Bianco et al.
5,441,516 A	8/1995	Wang et al.	5,649,952 A	7/1997	Lam
5,441,947 A	8/1995	Dodge et al.	5,649,977 A	7/1997	Campbell
5,443,458 A	8/1995	Eury	5,651,174 A	7/1997	Schwartz et al.
5,443,477 A	8/1995	Marin et al.	5,652,243 A	7/1997	Bianco et al.
5,443,496 A	8/1995	Schwartz et al.	5,653,747 A	8/1997	Dereume 623/1.54
5,443,498 A	8/1995	Fontaine	5,653,992 A	8/1997	Bezwada et al.
5,443,500 A	8/1995	Sigwart	5,662,609 A	9/1997	Slepian
5,447,724 A	9/1995	Heimus et al.	5,665,591 A	9/1997	Sonenshein et al. 435/375
5,449,372 A	9/1995	Schmaltz et al.	5,665,728 A	9/1997	Morris et al.
5,449,373 A	9/1995	Pinchaski et al.	5,667,764 A	9/1997	Kopia et al. 424/1.45
5,449,382 A	9/1995	Dayton	5,669,924 A	9/1997	Shaknovich
5,464,450 A	11/1995	Buscemi et al.	5,670,506 A	9/1997	Leigh et al.
5,464,540 A	11/1995	Friesen et al. 210/640	5,672,638 A	9/1997	Verhoeven et al. 523/112
5,464,650 A	11/1995	Berg et al.	5,674,242 A	10/1997	Phan et al. 606/198
5,474,563 A	12/1995	Myler et al. 606/108	5,679,400 A	10/1997	Tuch
5,486,357 A	1/1996	Narayanan	5,679,659 A	10/1997	Verhoeven et al.
5,496,365 A	3/1996	Sgro	5,684,061 A	11/1997	Ohnishi et al. 523/114
5,500,013 A	3/1996	Buscemi et al.	5,691,311 A	11/1997	Maraganore et al. 514/12
5,504,091 A	4/1996	Molnar-Kimber et al. ... 514/291	5,693,085 A	12/1997	Buirge et al.
5,510,077 A	4/1996	Dinh et al.	5,697,967 A	12/1997	Dinh et al.
5,512,055 A	4/1996	Domb et al. 604/265	5,697,971 A	12/1997	Fischell et al.
5,516,781 A	5/1996	Morris et al.	5,700,286 A	12/1997	Tartaglia et al.
5,519,042 A	5/1996	Morris et al. 514/378	5,707,385 A	1/1998	Williams
5,523,092 A	6/1996	Hanson et al.	5,709,874 A	1/1998	Hanson et al.
5,527,354 A	6/1996	Fontaine et al.	5,713,949 A	2/1998	Jayaraman 623/1.12
5,545,208 A	8/1996	Wolff et al.	5,716,981 A	2/1998	Hunter et al. 514/449
5,551,954 A	9/1996	Buscemi et al.	5,725,549 A	3/1998	Lam
5,554,182 A	9/1996	Dinh et al.	5,725,567 A	3/1998	Wolff et al.
5,554,954 A	9/1996	Takahashi	5,728,150 A	3/1998	McDonald et al.
5,556,413 A	9/1996	Lam	5,728,420 A	3/1998	Keogh
5,559,122 A	9/1996	Nelson et al. 514/291	5,731,326 A	3/1998	Hart et al.
5,562,922 A	10/1996	Lambert	5,733,327 A	3/1998	Igaki et al.
5,563,146 A	10/1996	Morris et al.	5,733,920 A	3/1998	Mansuri et al.
5,569,197 A	10/1996	Helmus et al.	5,733,925 A	3/1998	Kunz et al.
5,569,295 A	10/1996	Lam	5,735,897 A	4/1998	Buirge
5,569,462 A	10/1996	Martinson et al. 424/423	5,739,138 A	4/1998	Bianco et al.
5,569,463 A	10/1996	Helmus et al. 424/426	5,755,734 A	5/1998	Richter et al.
5,571,089 A	11/1996	Crocker 604/103.01	5,755,772 A	5/1998	Evans et al. 128/898
5,571,166 A	11/1996	Dinh et al.	5,759,205 A	6/1998	Valentini 433/173
5,574,059 A	11/1996	Regunathan et al.	5,769,883 A	6/1998	Buscemi et al.
5,575,818 A	11/1996	Pinchuk 623/1.15	5,776,184 A	7/1998	Tuch
5,578,075 A	11/1996	Dayton	5,780,462 A	7/1998	Lee et al. 514/183
5,580,873 A	12/1996	Bianco et al.	5,780,476 A	7/1998	Undercriner et al.
5,580,874 A	12/1996	Bianco et al.	5,782,908 A	7/1998	Cahalan et al.
5,591,140 A	1/1997	Narayanan et al.	5,788,979 A	8/1998	Alt
5,591,197 A	1/1997	Orth et al.	5,792,106 A	8/1998	Mische 604/103.01

US 7,300,662 B2

Page 4

5,792,772 A	8/1998	Bianco et al.	6,179,817 B1	1/2001	Zhong	604/265	
5,798,372 A	8/1998	Davies et al.	6,187,757 B1	2/2001	Clackson et al.	514/31	
5,799,384 A	9/1998	Schwartz et al.	6,193,746 B1	2/2001	Strecker	623/1.13	
5,800,507 A	9/1998	Schwartz	6,214,901 B1	4/2001	Chudzik et al.		
5,800,508 A	9/1998	Goicoechea et al.	6,225,346 B1	5/2001	Tang et al.	514/523	
5,807,861 A	9/1998	Klein et al.	6,240,616 B1	6/2001	Yan		
5,811,447 A	9/1998	Kunz et al.	6,245,537 B1	6/2001	Williams et al.	435/135	
5,820,917 A	10/1998	Tuch	6,251,920 B1	6/2001	Grainger et al.	514/319	
5,820,918 A	10/1998	Ronan et al.	6,254,632 B1	7/2001	Wu et al.		
5,824,048 A	10/1998	Tuch	6,254,634 B1	7/2001	Anderson et al.	623/1.42	
5,824,049 A	10/1998	Ragheb et al.	6,258,121 B1	7/2001	Yang et al.		
5,827,587 A	10/1998	Fukushi	428/36.6	7/2001	Kunz		
5,833,651 A	11/1998	Donovan et al.	6,273,913 B1	8/2001	Wright et al.		
5,837,008 A	11/1998	Berg et al.	6,284,305 B1	9/2001	Ding et al.	427/2.28	
5,837,313 A	11/1998	Ding et al.	6,287,320 B1	9/2001	Slepian		
5,843,120 A	12/1998	Israel et al.	623/1.15	9/2001	Hossainy et al.		
5,843,166 A	12/1998	Lentz et al.	623/1.13	10/2001	Ragheb et al.		
5,843,172 A	12/1998	Yan		10/2001	Sydney et al.	606/108	
5,849,034 A	12/1998	Schwartz		10/2001	Barry et al.		
5,851,217 A	12/1998	Wolff et al.		10/2001	Whitbourne		
5,851,231 A	12/1998	Wolff et al.		10/2001	Kunz et al.		
5,858,990 A	1/1999	Walsh		10/2001	Larson et al.		
5,861,027 A	1/1999	Trapp		10/2001	Hsu et al.		
5,865,814 A	2/1999	Tuch		11/2001	Caggiano et al.		
5,871,535 A	2/1999	Wolff et al.		11/2001	Ding et al.	424/423	
5,873,904 A	2/1999	Ragheb et al.		1/2002	Kamath et al.	424/423	
5,876,433 A	3/1999	Lunn		3/2002	Ding et al.	427/2.24	
5,877,224 A	3/1999	Broccini et al.	514/772.2	4/2002	Palasis et al.	424/93.2	
5,879,697 A	3/1999	Ding et al.		4/2002	Yang	623/1.42	
5,882,335 A	3/1999	Leone et al.		5/2002	Alt	623/1.15	
5,891,108 A	4/1999	Leone et al.		6/2002	Kinsella et al.	514/449	
5,893,840 A	4/1999	Hull et al.	604/103.02	6/2002	Schafer	514/19	
5,897,911 A	4/1999	Loeffler	427/2.25	6,517,858 B1	2/2003	Le Moel et al.	424/424
5,900,246 A	5/1999	Lambert		6,517,889 B1	2/2003	Jayaraman	427/2.24
5,902,266 A	5/1999	Leone et al.		6,545,097 B2	4/2003	Pinchuk et al.	525/240
5,912,253 A	6/1999	Cottens et al.	514/291	6,585,764 B2	7/2003	Wright et al.	623/1.42
5,916,910 A	6/1999	Lai	514/423	6,620,194 B2	9/2003	Ding et al.	623/1.43
5,922,393 A	7/1999	Jayaraman	427/2.3	6,746,773 B2	6/2004	Llanos et al.	428/421
5,922,730 A	7/1999	Hu et al.	514/291	6,776,796 B2	8/2004	Falotico et al.	623/1.46
5,932,243 A	8/1999	Fricker et al.	424/450	6,808,536 B2	10/2004	Wright et al.	623/1.42
5,932,299 A	8/1999	Katoot	427/508	2001/007083 A1	7/2001	Roorda	
5,932,580 A	8/1999	Levitzki et al.	181/152	2001/0029351 A1	10/2001	Falotico et al.	604/103.02
5,951,586 A	9/1999	Berg et al.		2001/0029660 A1	10/2001	Johnson	
5,957,971 A	9/1999	Schwartz		2001/0032014 A1	10/2001	Yang et al.	
5,968,091 A	10/1999	Pinchuk et al.	623/1.16	2001/0034363 A1	10/2001	Li et al.	
5,972,027 A	10/1999	Johnson		2001/0037145 A1	11/2001	Guruwaiya et al.	
5,976,534 A	11/1999	Hart et al.		2002/0010418 A1	1/2002	Lary et al.	604/101.04
5,977,163 A	11/1999	Li et al.		2002/0032477 A1	3/2002	Helmus et al.	623/1.2
5,980,553 A	11/1999	Gray et al.		2002/0041899 A1	4/2002	Chudzik et al.	424/487
5,980,566 A	11/1999	Alt et al.		2002/0061326 A1	5/2002	Li et al.	424/424
5,980,972 A	11/1999	Ding		2002/0068969 A1	6/2002	Shanley et al.	623/1.16
5,981,568 A	11/1999	Kunz et al.		2002/0071902 A1	6/2002	Ding et al.	427/2.24
5,985,307 A	11/1999	Hanson et al.		2002/0082680 A1	6/2002	Shanley et al.	623/1.16
5,997,468 A	12/1999	Wolff et al.		2002/0082685 A1	6/2002	Sirhan et al.	623/1.42
6,004,346 A	12/1999	Wolff et al.		2002/0091433 A1	7/2002	Ding et al.	623/1.2
6,015,432 A	1/2000	Rakos et al.	623/1.13	2002/0095114 A1	7/2002	Palasis	604/96.01
6,015,815 A	1/2000	Mollison	514/291	2002/0099438 A1	7/2002	Furst	623/1.16
6,039,721 A	3/2000	Johnson et al.		2002/0103526 A1	8/2002	Steinke	623/1.11
6,059,813 A	5/2000	Vrba et al.		2002/0119178 A1	8/2002	Levesque et al.	424/423
6,071,305 A	6/2000	Brown et al.		2002/0123505 A1	9/2002	Mollison et al.	514/291
6,074,659 A	6/2000	Kunz et al.		2002/0127327 A1	9/2002	Schwartz et al.	427/2.15
6,080,190 A	6/2000	Schwartz		2002/0132222 A1	9/2002	Das	623/1.16
6,096,070 A	8/2000	Ragheb et al.		2002/013224 A1	9/2002	Bajgar et al.	623/1.39
6,120,536 A	9/2000	Dinge et al.		2002/0165608 A1	11/2002	Llanos	604/500
6,120,847 A	9/2000	Yang et al.	427/335	2002/0193475 A1	12/2002	Hossainy et al.	524/113
6,136,798 A	10/2000	Cody et al.		2003/0065377 A1	4/2003	Davila et al.	604/265
6,140,127 A	10/2000	Sprague		2003/0216699 A1	11/2003	Falotico	
6,146,358 A	11/2000	Rowe		2004/0049265 A1	3/2004	Ding et al.	623/1.42
6,153,252 A	11/2000	Hossainy et al.		2004/0243097 A1	12/2004	Falotico et al.	604/500
6,159,488 A	12/2000	Nagier et al.	424/423	2004/0260268 A1	12/2004	Falotico et al.	604/500
6,171,232 B1	1/2001	Papandreu et al.		2005/002986 A1	1/2005	Falotico et al.	424/426
6,171,609 B1	1/2001	Kunz		2005/004663 A1	1/2005	Llanos et al.	623/1.46
6,177,272 B1	1/2001	Nabel et al.		2005/0033261 A1	2/2005	Falotico et al.	604/500

US 7,300,662 B2

Page 5

2005/0106210 A1	5/2005	Ding et al.	424/423	WO	01/87372 A1	11/2001
2005/0187611 A1	8/2005	Ding et al.	623/1.15	WO	01/87373 A1	11/2001
2005/0208200 A1	9/2005	Ding et al.	427/2.25	WO	WO 01/87376 A1	11/2001
2006/0088654 A1	4/2006	Ding et al.	427/2.21	WO	02/26139 A1	4/2002
2006/0089705 A1	4/2006	Ding et al.	623/1.15	WO	02/26271 A1	4/2002
FOREIGN PATENT DOCUMENTS							
DE	19723723 A1	12/1998			WO	02/26280 A1	4/2002
EP	0 145 166 A2	6/1985			WO	02/26281 A1	4/2002
EP	0 177 330 A2	4/1986				03/015664 A1	2/2003
EP	0 183 372 A1	6/1986				03/057218 A1	7/2003
EP	0 221 570 A2	5/1987					
EP	0 421 729 A2	4/1991					
EP	0 540 290 A2	10/1992					
EP	0 568 310 A1	11/1993					
EP	0 604 022 A1	6/1994					
EP	0 621 015 A1	10/1994					
EP	0 623 354 A1	11/1994					
EP	0 734 698 A2	3/1996					
EP	0 712 615 A1	5/1996					
EP	0 716 836 A1	6/1996					
EP	0 800 801 A1	8/1996					
EP	0 734 721 A1	10/1996					
EP	0 747 069 A2	12/1996					
EP	0 761 251 A1	3/1997					
EP	0 830 853 A1	7/1997					
EP	0 540 290 B1	1/1998					
EP	0 815 803 A1	7/1998					
EP	0 850 651 A2	7/1998					
EP	0 938 878 A3	9/1999					
EP	0950386 B1	10/1999					
EP	0 968 688 A1	1/2000					
EP	0 633 032 B1	2/2001					
EP	1 192 957 A2	4/2002					
EP	1 588 726 A1	10/2005					
EP	1 588 727 A1	10/2005					
FR	0 566 807 A1	4/1992					
GB	1 205 743	9/1970					
GB	2 135 585 A	9/1984					
GB	0 662 307 A2	12/1994					
SU	660689	5/1979					
SU	1457921	2/1989					
WO	89/03232 A1	4/1989					
WO	WO 91/12779 A1	9/1991					
WO	WO 92/15286 A1	9/1992					
WO	WO 94/01056 A1	1/1994					
WO	WO 94/21308 A1	9/1994					
WO	WO 94/21309 A1	9/1994					
WO	WO 94/24961 A1	11/1994					
WO	WO 96/00272 A1	1/1996					
WO	WO 96/26689 A1	9/1996					
WO	WO 96/32907 A1	10/1996					
WO	WO 96/34580 A1	11/1996					
WO	96/41807 A1	12/1996					
WO	WO 97/25000 A1	7/1997					
WO	WO 97/33534 A1	9/1997					
WO	97/35575 A1	10/1997					
WO	98/08463 A1	3/1998					
WO	WO 98/13344 A1	4/1998					
WO	WO 98/19628 A1	5/1998					
WO	98/23244 A1	6/1998					
WO	WO 98/23228 A1	6/1998					
WO	WO 98/34669 A1	8/1998					
WO	WO 98/36784 A1	8/1998					
WO	WO 98/47447 A1	10/1998					
WO	WO 98/56312 A1	12/1998					
WO	00/21584 A1	4/2000					
WO	00/27455 A1	5/2000					
WO	WO 00/27445 A1	5/2000					
WO	00/32255 A1	6/2000					
WO	00/38754 A1	7/2000					
WO	01/87342 A2	11/2001					
OTHER PUBLICATIONS							
U.S. Appl. No. 07/819,314, filed Jan. 9, 1992, Morris.							
U.S. Appl. No. 08/424,884, filed Apr. 19, 1995, Helmus et al.							
U.S. Appl. No. 08/526,273, filed Sep. 11, 1995, Ding.							
U.S. Appl. No. 08/730,542, filed Oct. 11, 1996, Helmus.							
U.S. Appl. No. 09/575,480, filed May 19, 2000, Kopia.							
U.S. Appl. No. 10/431,059, filed May 7, 2003, Falotico.							
Abraham, R. T., "Mammalian target of rapamycin: Immunosuppressive drugs offer new insight into cell growth regulation," <i>Progress in Inflammation Research</i> , 2000, Switzerland.							
Alvarado, R. et al., "Evaluation of Polymer-coated Balloon-expandable Stents in Bile Ducts," <i>Radiology</i> , 1989, 170, 975-978.							
Badimon, J. J. et al., "Inhibitory Effects of Rapamycin on Intimal Hyperplasia After PTCA," <i>JACC</i> , Mar. 1998.							
Bailey et al., "Polymer Coating of Palmaz-Schatz Stent Attenuates Vascular Spasm after Stent Placement," <i>Circulation</i> , 82:III-541 (1990).							
Berk, B. C. et al., "Pharmacologic Roles of Heparin and Glucocorticoids to Prevent Restenosis After Coronary Angioplasty," <i>JACC</i> , May 1991, 17(6), 111B-117B.							
Bertram, P. G. et al., "The 14-3-3 proteins positively regulate rapamycin-sensitive signaling," <i>Current Biology</i> , 1998, 8, 1259-1267.							
Biomaterials Science (B.D. Ratner, Ed.), Academic Press, New York, NY, pp. 228-238, 1996.							
Campbell, G. R. et al., "Phenotypic Modulation of Smooth Muscle Cells in Primary Culture, Vascular Smooth Muscle Cells in Culture," <i>CRC Press</i> , 1987, 39-55.							
Chang, M. W. et al., "Adenovirus-mediated Over-expression of the Cyclin/Cyclin-dependent Kinase inhibitor, p21 inhibits Vascular Smooth Muscle Cell Proliferation and Neointima Formation in the Rat Carotid Artery Model of Balloon Angioplasty," <i>J. Clin. Invest.</i> , 1995, 96, 2260-2268.							
Chung, J. et al., "Rapamycin-FKBP specifically blocks growth-dependent activation of and signaling by the 70 kd S6 protein kinases," <i>Cell</i> , Jun. 26, 1992, 69(7), 1227-1236.							
Clowes, A. W. et al., "Kinetics of cellular proliferation after arterial injury. IV. Heparin inhibits rat smooth muscle mitogenesis and migration," <i>Circ. Res.</i> , 1986, 58(6), 839-845.							
Clowes, A. W. et al., Kinetics of Cellular Proliferation after Arterial Injury, <i>Laboratory Investigation</i> , 1985, 52(6), 611-616.							
Clowes, A. W. et al., "Significance of quiescent smooth muscle migration in the injured rat carotid artery," <i>Circ Res.</i> 1985, 56(1), 139-145.							
Clowes, A. W., "Suppression by heparin of smooth muscle cell proliferation in injured arteries," <i>Nature</i> , 1977, 265(5595), 625-626.							
Colburn, M. D. et al., "Dose responsive suppression of myointimal hyperplasia by dexamethasone," <i>J. Vasc. Surg.</i> , 1992, 15, 510-518.							
Currier, J. W. et al., "Colchicine Inhibits Restenosis After Iliac Angioplasty in the Atherosclerotic Rabbit," <i>Circ.</i> , 1989, 80(4), 11-66 (Abstract No. 0263).							
Encyclopedia of Polymer Science and Engineering, vol. 7, Fluococarbon Elastomers, p. 257-267, Mar. 1989.							
Farb, A. et al., "Vascular smooth muscle cell cytotoxicity and sustained inhibition of neointimal formation by fibroblast growth factor 2-saporin fusion protein," <i>Circ. Res.</i> , 1997, 80, 542-550.							
Ferns, G. A. A. et al., "Inhibition of Neointimal Smooth Muscle Accumulation After Angioplasty by an Antibody to PDGF," <i>Science</i> , 1991, 253, 1129-1132.							

US 7,300,662 B2

Page 6

- Fischman, D. L. et al., "A Randomized Comparison of Coronary-Stent Placement and Balloon Angioplasty in the Treatment of Coronary Artery Disease," *N. Eng. J. Med.*, Aug. 25, 1994, 331(8), 496-501.
- Franklin, S. M. et al., "Pharmacologic prevention of restenosis after coronary angioplasty: review of the randomized clinical trials," *Coronary Artery Disease* Mar. 1993, 4(3), 232-242.
- Fukuyama, J. et al., "Tranilast suppresses the vascular intimal hyperplasia after balloon injury in rabbits fed on a high-cholesterol diet," *Eur. J. Pharmacol.*, 1996, 318, 327-332.
- Gregory, C. R. et al., "Rapamycin Inhibits Arterial Intimal Thickening Caused by Both Alloimmune and Mechanical Injury," *Transplantation*, Jun. 1993, 55(6), 1409-1418.
- Gregory, C. R. et al., "Treatment with Rapamycin and Mycophenolic Acid Reduces Arterial Intimal Thickening Produced by Mechanical Injury and Allows Endothelial Replacement," *Transplantation*, Mar. 15, 1995, 59(5), 655-661.
- Guyton, J. R. et al., "Inhibition of rat arterial smooth muscle cell proliferation by heparin. In vivo studies with anticoagulant and nonanticoagulant heparin," *Circ. Res.*, 1980, 46, 625-634.
- Hansson, G. K. et al., "Interferon- γ Inhibits Arterial Stenosis After Injury," *Circ.*, 1991, 84, 1266-1272.
- Hashemolhosseini, S. et al., "Rapamycin Inhibition of the G1 to S Transition Is Mediated by Effects on Cyclin D1 mRNA and Protein Stability," *J. Biol. Chem.*, Jun. 5, 1998, 273, 14424-14429.
- Jonasson, J. et al., "Cyclosporin A inhibits smooth muscle proliferation in the vascular response to injury," *Proc. Natl. Acad. Sci.*, 1988, 85, 2303-2306.
- Kuhnt, M. et al., "Microbial Conversion of Rapamycin," *Enzyme and Microbial Technology*, 1997, 21, 405-412.
- Lange, R. A. MD et al., "Restenosis After Coronary Balloon Angioplasty," *Annu. Rev. Med.*, 1991, 42, 127-132.
- Liu, M. W. et al., "Trapidil in Preventing Restenosis After Balloon Angioplasty in the Atherosclerotic Rabbit," *Circ.*, 1990, 81, 1089-1093.
- Liu, M. W. MD et al., "Restenosis After Coronary Angioplasty: Potential Biologic Determinants and Role of Intimal Hyperplasia," *Circulation*, 1989, 79, 1374-1387.
- Lundergan, C. F. et al., "Peptide inhibition of Myointimal Proliferation by Angiopeptin, a Somatostatin Analogue," *JACC*, May 1991, 17(6), 132B-136B.
- Majesky, M. W. et al., "Heparin regulates smooth muscle S phase entry in the injured rat carotid artery," *Circ. Res.*, 1987, 61, 296-300.
- Marx, S. O. et al., "Rapamycin-FKBP Inhibits Cell Cycle Regulators of Proliferation in Vascular Smooth Muscle Cells," *Circ. Res.*, 1995, 76, 412-417.
- Nemecek, G. M. et al., "Terbinafine Inhibits the Mitogenic Response to Platelet-Derived Growth Factor in Vitro and Neointimal Proliferation in Vivo," *J. Pharmacol. Exp. Thera.*, 1989, 248, 1167-1174.
- Okada, T. et al., "Localized Release of Perivascular Heparin Inhibits Intimal Proliferation after Endothelial Injury without Systemic Anticoagulation," *Neurosurgery*, 1989, 25, 892-898.
- Poon, M. et al., "Rapamycin Inhibits Vascular Smooth Muscle Cell Migration," *J. Clin. Invest.*, Nov. 1996, 98(10), 2277-2283.
- Popma, J. J. et al., "Clinical trials of restenosis after coronary angioplasty," *Circulation*, Sep. 1991, 84(3), 1426-1436.
- Powell, J. S. et al., "Inhibitors of Angiotensin-Converting Enzyme Prevent Myointimal Proliferation After Vascular Injury," *Science*, 1989, 245, 186-188.
- Rensing, B. J. et al., "Coronary restenosis elimination with a sirolimus eluting stent," *European Heart Journal*, 2001, 22, 2125-2130.
- Rodeck, C. et al., "Methods for the Transcervical Collection of Fetal Cells During the First Trimester of Pregnancy," *Prenatal Diagnosis*, 1995, 15, 933-942.
- Serruys, P. W. et al., "A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease," *N Engl J Med*, Aug. 25, 1994; 331(8), 489-495.
- Serruys, P. W. et al., "Evaluation of ketanserin in the prevention of restenosis after percutaneous transluminal coronary angioplasty. A multicenter randomized double-blind placebo-controlled trial," *Circulation*. Oct. 1993; 88(4 Pt 1), 1588-1601.
- Serruys, P. W. et al., "Heparin-coated Palmaz-Schatz stents in human coronary arteries. Early outcome of the Benestent-II Pilot Study," *Circulation*, Feb. 1, 1996; 93(3), 412-422.
- Siekierka, J. J., "Probing T-Cell Signal Transduction Pathways with the Immunosuppressive Drugs, FK-506 and Rapamycin," *Immunologic Research*, 1994, 13, 110-116.
- Sigwart, et al., "Intravascular Stents to Prevent Occlusion and Restenosis After Transluminal Angioplasty," *N. Engl. J. Med.*, Mar. 19, 1987, 316, 701-706.
- Simons, M. et al., "Antisense c-myb oligonucleotides inhibit intimal arterial smooth muscle cell accumulation in vivo," *Nature*, 1992, 359, 67-70.
- Snow, A. D. et al., "Heparin modulates the composition of the extracellular matrix domain surrounding arterial smooth muscle cells," *Am. J. Pathol.*, 1990, 137, 313-330.
- Sollott, S. J. et al., "Taxol Inhibits Neointimal Smooth Muscle Cell Accumulation after Angioplasty in the Rat," *J. Clin. Invest.*, 1995, 95, 1869-1876.
- van Der Giessen, et al., "Self-expandable Mesh Stents: an Experimental Study Comparing Polymer Coated and Uncoated Wallstent Stents in the Coronary Circulation of Pigs," *Circulation* 1990, 82(suppl. III):III-542.
- van Der Giessen, W. J. et al., "Coronary stenting with polymer-coated and uncoated self-expanding endoprostheses in pigs," *Coron. Art. Disease* 1992; 3, 631-640.
- Vasey, C. G. et al., "Clinical Cardiology: Stress Echo and Coronary Flow", , *Circulation*, Oct. 1989, 80(4) Supplement II, II-66.
- Verweire, E. et al., "Evaluation of Fluorinated Polymers As Coronary Stent Coating," *Journal of Materials Science: Materials in medicine*, Apr. 2000.
- Weinberger, J. et al., "Intracoronary irradiation: dose response for the prevention of restenosis in swine," *Int. J. Rad. Onc. Biol. Phys.*, 1996, 36, 767-775.
- Preliminary Amendment in U.S. Appl. No. 07/258,189, May 22, 1989.
- Trial Transcript from Nov. 6, 2000 at 185-90 and 235-36 (Attorney's opening remarks regarding '984 patent).
- Trial Transcript from Nov. 7, 2000 at 274-301, 307-315, 320-28 and 332 (Cordis expert testimony regarding the Palmaz-Schatz stent); 370-379, 480-496 (J. Palmaz testimony regarding the Palmaz-Schatz stent, the '984 patent and the connected z-stent art).
- Trial Transcript from Nov. 8, 2000 at 547-63, 657-63, 674-722, 782-85 (Cordis expert testimony regarding the Palmaz-Schatz stent, the '984 patent and the connected z-stent art).
- Trial Transcript from Nov. 9, 2000 at 819-23, 921 (Cordis expert testimony regarding the '984 patent); 926-941 (R. Croce testimony re Palmaz-Schatz stent); 1033-1053 (R. Schatz testimony).
- Trial Transcript from Nov. 13, 2000 at 1086-1134 (R. Schatz testimony); 1275-1305 (Cordis expert testimony regarding the '984 patent).
- Trial Transcript from Nov. 14, 2000 at 1390-1404, 1448-1454, 1486-1500 (Cordis expert testimony regarding the '984 patent).
- Trial Transcript from Nov. 15, 2000 at 1686-87, 1724-42, 1828-34, 1850-54, 1887-92 (AVE expert testimony regarding the '984 patent).
- Trial Transcript from Nov. 16, 2000 at 2077-198 (AVE expert testimony regarding the alleged obviousness of the '984 patent).
- Trial Transcript from Nov. 17, 2000 at 2331-34 (jury instructions as to the meaning of the limitations of the claims of the '984 patent).
- Trial Transcript from Nov. 20, 2000 at 2441-48, 2499-2500, 2546-50, 2552-56 (Attorney's closing arguments regarding the '984 patent).
- Trial Transcript from Nov. 21, 2000 at 2592-94 (reading of jury verdict).
- Trial Transcript from Dec. 18, 2000 at 2750-95 (Cordis expert testimony regarding the Palmaz-Schatz stent during the damages phase).
- Trial Transcript from Dec. 20, 2000 at 3421-88 (AVE expert testimony regarding the Palmaz-Schatz stent during the damages phase).
- Jury verdict, dated Nov. 21, 2000.
- District Court decisions on post-trial motions (194 F. Supp. 2d 323). Court of Appeal for the Federal Circuit decision (339 F.3d 1352).

US 7,300,662 B2

Page 7

Trial Transcript from Mar. 4, 2005 at 133-135, 171-173 and 192-96 (Attorney's opening remarks regarding '984 validity).

Trial Transcript from Mar. 7, 2005 at 275-31 1 (Cordis expert testimony regarding the Palmaz-Schatz stent); 342-46, 353-59, 416-425 (J. Palmaz testimony regarding the Palmaz-Schatz stent, the '984 patent and the connected z-stent art); 430-449, 452-58, 462-492 (R. Croce testimony regarding the Palmaz-Schatz stent); 500-507 (Cordis expert testimony regarding the '984 patent).

Trial Transcript from Mar. 8, 2005 at 609 (Cordis expert testimony regarding the '984 patent); 628-73, 724-740, 773, 801-839 (Cordis expert testimony regarding the '984 patent, the prior art and the Palmaz-Schatz stent).

Trial Transcript from Mar. 9, 2005 at 936-49, 968-69 (Cordis expert testimony regarding the '984 patent, the prior art and the Palmaz-Schatz stent).

Trial Transcript from Mar. 10, 2005 at 1427-74, 178-1509, 1514-23 (AVE expert testimony regarding the alleged obviousness of the '984 patent); 1566-93 (AVE expert testimony regarding Palmaz-Schatz stent); 1634-49 (R. Schatz testimony).

Trial Transcript from Mar. 11, 2005 at 1846-47, 1891-1900, 1919 (Attorneys' closing arguments regarding '984 obviousness).

Trial Transcript from Mar. 14, 2005 at 1964-67 (reading of jury verdict).

Jury verdict dated Mar. 14, 2005.

Medtronic Vascular Inc.'s Opening Brief in Support of Its Motion for Judgment As A Infringement Claim dated Apr. 19, 2005.

Medtronic Vascular Inc.'s Opening Brief in Support of Its Motion for a New Trial dated Apr. 19, 2005.

D.I. 1407, Cordis' Combined Answering Brief In Opposition to AVE's Motion for JMOL on Infringement of the Palmaz '762 and Schatz '984 Patents and Its Motion for a New Trial dated May 5, 2005.

D.I. 1414, Medtronic Vascular Inc.'s Combined Reply Brief In Support of Its Motion for Judgment as a Matter of Law on Cordis Corp.'s Patent Infringement Claims and Its Motion for a New Trial dated May 19, 2005.

Trial Transcript from Feb. 8, 2001 at 372-412, 449-469 (B. Tobor testimony regarding the prosecution of the '417, '984 and '332 patents); 510-13 (J. Milnarrow testimony regarding the prosecution of the '332 patent); 558-604 (J. Palmaz testimony regarding the prosecution of the '417, '984 and '332 patents and the prior art).

Trial Transcript from Feb. 9, 2001 at 637-45, 662-672, 682-85 (J. Palmaz testimony regarding the prior art); 699-742 (R. Schatz testimony); 769-770, 790-95 (Cordis expert testimony regarding prior art).

D.I. 1067, Medtronic AVE, Inc.'s Post-Trial Brief Relating to the Unenforceability of the '762 and '984 Patents Due to Inequitable Conduct.

D.I. 1077, Cordis' Combined Answering Brief in Opposition to AVE's BSC's Post-Hearing Briefs on Alleged Inequitable Conduct Concerning the '762, '984 and '332 Patents.

D.I. 1089, Reply Brief In Support of Medtronic AVE, Inc.'s Contention that the '762 and '984 Patents are Unenforceable Due to Inequitable Conduct dated May 7, 2001.

C.A. No. 00-886-SLR, Answer and Counterclaims of Def. Medtronic AVE, Inc. To First Amended Complaint of Plaintiff Cordis Corp.

BSC's Opening Post-Trial Brief in Support of Its Defense That the Patents in Suit Are Unenforceable, dated Mar. 16, 2001.

Reply Brief in Support of BSC's Defense That the Patents in Suit Are Unenforceable, dated May 7, 2001.

Court's Decision on allegations of inequitable conduct (194 F. Supp. 2d 323) Mar. 28, 2002.

Trial Transcript from Nov. 21, 2000 at 155-57 and 180-84 (Attorneys' opening remarks regarding '332 patent).

Trial Transcript from Nov. 27, 2000 at 227-51, 260-300 (Cordis expert testimony regarding the Palmaz-Schatz stent); 343-60, 363-67, 424-33 (J. Palmaz testimony regarding the Palmaz-Schatz stent and the '332 patent).

Trial Transcript from Nov. 28, 2000 at 649-71.

Trial Transcript from Nov. 29, 2000 at 791-816, 859-870, 953-62 (Cordis expert testimony regarding the '332 patent and the Palmaz-Schatz stent).

Trial Transcript from Nov. 30, 2000 at 1018 (Cordis expert testimony regarding the '332 patent); 1062-80, 1108-1111 (R. Croce testimony regarding the Palmaz-Schatz stent); 1169-70, 1205-17, 1236-45 (Cordis expert testimony regarding the '332 patent).

Trial Transcript from Dec. 1, 2000 at 1352-54 (Cordis expert testimony regarding the '332 patent); 1364-1442 (R. Schatz testimony); 1493-1508, 1552-69 (BSC expert testimony regarding the '332 patent and the Palmaz-Schatz stent).

Trial Transcript from Dec. 4, 2000 at 1602-12, 1638-51, 1713-14, 1730-61, 1811-14, 1823-36 (BSC expert testimony regarding the alleged obviousness of the '332 patent, the prior art and the Palmaz-Schatz stent).

Trial Transcript from Dec. 6, 2000 at 2318-27, 2342-58 (BSC expert testimony regarding the '332 patent).

Trial Transcript from Dec. 7, 2000 at 2549-52 (Cordis expert testimony regarding the '332 patent); 2575-2579, 2591-92, 2630-31, 2649, 2669-71, 2684-85, 2688, 2708-10, 2725-27 (Attorney closing argument regarding '332 patent); 2742-46 Q'ury instructions as to the meaning of the limitations fo the claims of the '332 patent).

Trial Transcript from Dec. 11, 2000 at 2817-22 (reading of jury verdict).

Jury verdict, dated Dec. 11, 2000.

D.I. 699, Motion by Defendant BSC and Scimed Life Systems, Inc. For Summary Judgment of Invalidity of U.S. Patent No. 5,902,332 dated Apr. 4, 2000.

D.I.896, Order Denying Motion for Summary Judgment of Invalidity and Unenforceability of Claims 1, 3, and 5 of the U.S. Patent No. 5,902,332 Denying {699-1} Motion for Summary Judgment of Invalidity of U.S. Patent No. 5,902,332 dated Oct. 12, 2000.

Wright et al., Percutaneous Endovascular Stent: An Experimental Study (Abstract), RSNA Meeting (Nov. 28, 1984).

Hearing Transcript from Feb. 10, 1998 at 122-32, 146-80 (Attorneys' opening remarks regarding '417 patent); 180-312 (R. Schatz testimony) [Portions of This Transcript Have Been Removed As Confidential].

Hearing Transcript from Feb. 11, 1998 at 427-575, 577-651 (Cordis expert testimony regarding the '417 patent, the prior art and the Palmaz-Schatz stent).

Hearing Transcript from Feb. 13, 1998 at 1121-1261 (Guidant expert testimony regarding the alleged obviousness of the '417 patent, the prior art and the Palmaz-Schatz stent). [Portions of This Transcript Have Been Removed As Confidential].

Order by J. Robinson denying Cordis' Motion for a Preliminary Injunction Against ACS dated Jul. 17, 1998.

ACS, Inc.'s and Guidant Corp.'s Opening Brief in Support of Their Motion for Summary Judgment of Invalidity of U.S. Patent No. 5,102,417 dated Aug. 27, 1998.

Plaintiffs' Answering Brief in Opposition to ACS' and BSC' Motion for Summary Judgment on Obviousness dated Sep. 24, 1998.

Order dated Mar. 31, 2000.

Schatz Deposition Testimony; May 15, 1996: 79-83, 89-92, 105-107 and 153-161.

Schatz Deposition Testimony; May 16, 1996: 555-564, 569-572.

Schatz Deposition Testimony; Jan. 18, 1998: 67-73, 108-110.

Schatz Deposition Testimony; Jul. 14, 1998: 69-77, 108-112, 119-123.

Schatz Deposition Testimony; Jul. 12, 1999: 88-91, 132-135, 144-149, 218-223, 231-242.

Schatz Deposition Testimony; Jul. 13, 1999: 251-334, 339-345, 374-416.

Schatz Deposition Testimony; Jul. 14, 1999: 454-550.

Schatz Deposition Testimony; Jul. 15, 1999: 560-614.

Schatz Deposition Testimony; Dec. 2, 1999: 906-911, 928-942, 945-963, 976-978, 1029-1034, 1038-1042.

Palmaz Deposition Testimony, Nov. 5, 1991: 160-172.

Palmaz Deposition Testimony, Feb. 5, 1995: 710-727.

Palmaz Deposition Testimony, Jul. 16, 1998: 55-56; 81-82.

Palmaz Deposition Testimony, Jul. 28, 1999: 560-568, 570-579.

Palmaz Deposition Testimony, Jul. 29, 1999: 778-785.

Palmaz Deposition Testimony, Aug. 31, 1999: 1403-1452.

Palmaz Deposition Testimony, Sep. 2, 1999: 1953-1960.

US 7,300,662 B2

Page 8

- Palmaz Deposition Testimony, Oct. 14, 1999: 2201-2209; 2275-2342; 2371-2411.
- Palmaz Deposition Testimony, Oct. 15, 1999: 2424-2497; 2508-2589.
- Palmaz Deposition Testimony, Oct. 16, 1999: 2853-2860.
- Tobor Deposition Testimony, Jun. 17, 1999: 837-958.
- Tobor Deposition Testimony, Jun. 18, 1999: 1095-1184.
- Tobor Deposition Testimony, Dec. 1, 1999: 1217-1371.
- Tobor Deposition Testimony, Dec. 2, 1999: 1398-1414; 1444-1508; 1532-1548.
- Tobor Deposition Testimony, Dec. 3, 1999: 1652-1653; 1662-1672; 1683-1694.
- Kula Deposition Testimony, Apr. 20, 1999: 268-169.
- Kula Deposition Testimony, Nov. 16, 1999: 660-675; 680-694; 748-755; 774-821.
- Kula Deposition Testimony, Nov. 18, 1999: 176-223.
- Expert Report of Dr. Rodney S. Badger on Behalf of Medtronic AVE, Inc. (Jan. 31, 2000).
- Expert Report of Dr. Joseph Bonn on Behalf of Medtronic AVE, Inc. (Jan. 31, 2000).
- Deposition of Dr. Joseph Bonn dated Mar. 14, 2000.
- Rebuttal Expert Report of Nigel Buller, B.Sc., M.D., F.R.C.P. (Mar. 2000).
- Second Supplemental Rebuttal Expert Report of Nigel Buller, B.Sc., M.B., F.R.C.P. (Aug. 17, 2004).
- Rebuttal Expert Report of John M. Collins, PH.D. (Feb. 2000).
- Expert Report of David C. Cumberland, M.D. (Jan. 24, 2000).
- Expert Report of John T. Goolkasian (Feb. 2000).
- Deposition of Richard R. Heuser, M.D. (Sep. 7, 2004).
- Deposition of Henry R. Piehler (Sep. 10, 2004).
- Deposition of Ronald J. Solar (Mar. 22, 2000).
- Deposition of Ronald J. Solar (Mar. 23, 2000).
- Deposition of Ronald J. Solar (Apr. 12, 2000).
- Expert Report of Dr. Arina Van Breda on Behalf of Medtronic AVE, Inc. (Jan. 31, 2000).
- Deposition of Arina Van Breda (Mar. 24, 2000).
- Deposition of Arina Van Breda (Aug. 21, 2004).
- Expert Report of John F. Witherspoon (Jan. 24, 2000).
- Supplemental Expert Report of John F. Witherspoon (Oct. 27, 2000).
- Deposition of John F. Witherspoon (Mar. 8, 2000).
- Palmaz et al., Article: Normal and Stenotic Renal Arteries: Experimental Balloon Expandable Intraluminal Stenting, Radiology, Sep. 1987. (AVE 84).
- Julio C. Palmaz, Article: "Expandable vascular endoprosthesis." (AVE 132).
- Duprat et. al., Article: Flexible Balloon-Expandable Stent for Small Vessels Duprat et. al. Radiology, vol. 162, pp. 276-278, 1987. (AVE 134).
- Coons et. al., Article: "Large-Bore, Long Biliary Endoprosthesis (Biliary Stents) for Improved Drainage," Radiology, vol. 148, pp. 89-94, 1983. (AVE 143).
- Honickman et al., Article: "Malpositioned Biliary Endoprosthesis, Technical Developments And Instrumentation," vol. 144, No. 2., 1982. (AVE 144).
- Harries-Jones, et al., Article: "Repositioning of Biliary Endoprosthesis with Gruntzig Balloon Catheters," AJR, vol. 138, pp. 771-772, 1982. (AVE 153).
- Charnsangavej et al., Article "Stenosis of the Vena Cava: Preliminary Assessment of Treatment with Expandable Metallic Stents," Radiology, vol. 161, pp. 295-298, 1986. (AVE 359).
- Article "Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications," Radiology, vol. 158, pp. 309-312, 1986. (AVE 364).
- T. Yoshioka, et al., AIR Article: "Self-Expanding Endovascular Graft: An Experimental Study in Dogs", vol. 151, pp. 673-676, 1988. (AVE 438).
- Article: "Expandable Intraluminal Vascular Graft: A Feasibility Study," Surgery, vol. 99, pp. 199-205, 1986. (AVE 461).
- Lawrence et al., Article: "Percutaneous Endovascular Graft: Experimental Evaluation." Radiology, vol. 163, pp. 357-360, 1987. (AVE 671).
- Palmaz et al., Article: Expandable Intraluminal Graft: A Preliminary Study, Nov. 17-22, 1985, Radiology, vol. 156, pp. 73-77, 1985. (AVE 1224).
- Fallone et al., "Elastic Characteristics of the Self-Expanding Metallic Stents," Investigative Radiology, vol. 23, pp. 370-376, 1988. (AVE 1953).
- Palmaz Paper Entitled "Research Project Expandable Vascular Endoprosthesis" May 18, 1983.
- Rousseau , et al., Publication: "Percutaneous Vascular Stent: Experimental Studies & Preliminary Clinical Results in Peripheral Arterial Diseases," in Inter. Angio, vol. 6, 153-161, 1987. (AVE 3303).
- Rousseau , et al., Publication: "Self-Expanding Endovascular Prostheses: An Experimental Study," Radiology, vol. 164, pp. 709-714, 1987. (AVE 3303).
- Wallace, et al., Article: "Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications," Radiology, vol. 58, pp. 309-312, 1986. (DBX 2938).
- Palmaz et al., Article: "Expandable Intraluminal Graft: A Preliminary Study," Radiology, vol. 156, pp. 73-77 (DBX 4595).
- Program for the 12th Annual Course on Diagnostic Angiography and Interventional Radiology Mar. 23-26, 1987 sponsored by The Society of Cardiovascular and Interventional Radiology (DBX 6235).
- Preliminary Motion for Judgment re: Wolff claims 1, 2-8, 10, 15 and 19 (DBX6759).
- Palmaz Declaration (DBX 7069).
- Letter from Gaterud to Dr. Palmaz dated Jul. 5, 1988 with attached document entitled: "Segmented, balloon-expandable stents." (DBX 7160).
- Duprat et al., Article: "Flexible Balloon-Expandable Stent For Small Vessels," Radiology, vol. 168, pp. 276-278, 1987 (PX 82). Drawing Sent to Bodic on Mar. 17, 1986 (PX 374).
- Letter from Dr. Palmaz to R. Bowman enclosing a model of the flexible coronary graft dated Mar. 17, 1986 (PX 337).
- Lab Notebook pages dated Jul. 30, 1987 from Rodney Wolff (COR 185596-597) (PX621A).
- Charnsangavej, et al., Article: "Stenosis of The Vena Cava Preliminary Assessment of Treatment with expandable Metallic Stents," Radiology, vol. 161, No. 2, pp. 295-298 with attached photographs, 1986. (API 72).
- J. Palmaz: The Current Status of Vascular Prostheses, published by SCIR in the Twelfth Annual Course on Diagnostic Angiography And Interventional Radiology Mar. 23-26, 1987. (API 73).
- Amendment in Response to Office Action of Oct. 18, 1988 in re: Application of Julio Palmaz S/N 174,246. (API 152).
- Article: Wallace, et al., Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications Work In Progress, Radiology, vol. 158, pp. 309-312. (API 295).
- Reply of Senior Party Schatz To Patentee Wolff's Opposition To The Belated Motion For Judgment Of Applicant Schatz With Regard To Wolff Claims 1, 2-8, 10, 11, 13-17, And 19 (COR 186450-455)(API 310).
- Brief Of Senior Party Schatz At Final Hearing (API 313).
- Letter from Ron Sickles to Ben Tobor dated Feb. 10, 1988 (Exhibit 42).
- Letter from R.O. Sickles to Mike Tatlow dated May 12, 1988 (Exhibit 43).
- Letter from R. O. Sickles to Richard Schatz dated Jun. 2, 1988 (Exhibit 44).
- Letter from Richard Schatz to Raimund Erbel dated Jun. 3, 1988 (Exhibit 45).
- Letter from Richard Schatz to Mike Schuler dated Aug. 29, 1991 (Exhibit 48).
- Minutes of J&J Stent Project Review Meeting dated Jan. 21, 1988 (Exhibit 7).
- Preliminary Motion for Judgment with Regard to Wolff Claims 1, 2-8, 10, 11, 13-17, and 19. (Exhibit 67).
- Declaration of Richard A Schatz. (Exhibit 75).
- Belated Motion for Judgement with Regard to Wolff Claims 1, 2-8, 10, 11, 13-17 and 19. (Schatz—Exhibit 77).
- Letter from Dr. Schatz to Mr. Tobor, dated Jun. 3, 1988. (Exhibit 122).

US 7,300,662 B2

Page 9

- Letter from Dr. Schatz to Mr. Romano, dated Nov. 28, 1988. (Exhibit 131).
- Letter from Mr. Sickles to Mr. Tobor, dated Feb. 10, 1988 (Exhibit 145).
- Richard A. Schatz, Article titled: "A View of Vascular Stents" Circulation, vol. 79, No. 2, pp. 445-457, 1989. (Exhibit 194).
- Senior Party Schatz's reply to Patente Wolff's Opposition to the Preliminary Motion Of Applicant Schatz for Judgment with regard to Wolff Claims 1, 2-8, 10, 11, and 13-17. (Exhibit 69).
- Wallace, et al., Article: "Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications' Work In Progress," Radiology, vol. 158, pp. 309-312, 1986. (Exhibit 165).
- Charnsangavej, et al., Article: "Stenosis of The Vena Cava Preliminary Assessment of Treatment with expandable Metallic Stents," Radioloby, vol. 161, No. 2, pp. 295-298 with attached photographs, 1986. (Exhibit 167).
- David D. Lawrence et al., Publication: Percutaneous Endovascular Graft: Experimental Evaluation¹, Radiology, pp. 357-360, 1987. (Exhibit 173).
- Charles E. Putnam, M.D., Cover and article from "Investigative Radiology", vol. 23, No. 5, May 1988. (Exhibit 177).
- Robert N. Berk, Cover and article from "American Journal of Roentgenology", pp. 673-676, 1988. (Exhibit 178).
- Declaration of John S. Kula Under 37 CFR § 1.672. (Kula—Exhibit 77).
- Yoshioka et al., Article: "Self-Expanding Endovascular Graft: An Experimental Study in Dogs" AJR, vol. 151, pp. 673-676, 1988. (PX 100).
- Palmaz, et al., Article: Expandable Intraluminal Graft: A Preliminary Study Work in Progress¹, Radiology, vol. 156, No. 1, pp. 73-77, 1985. (PX 101).
- Declaration of Richard Schatz Under 37 C.F.R. § 1.672. (PX 106).
- Charnsangavej et al., Article: "Stenosis of the Vena Cave: Preliminary Assessment of Treatment with Expandable Metallic Stents," Radiology, vol. 161, pp. 295-298, 1986. (PX 143).
- Wallace, et al., Article: Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications Work in Progress¹, Radiology, vol. 158, pp. 309-312, 1986. (PX 144).
- Gina Kolata, News Article: NY Times, "Devices That Opens Clogged Arteries Gets a Falling Grade in a New Study", pp. 16-18, Jan 3, 1991. (PX 186).
- Duprat, et al., Article: "Flexible Balloon- Expanded Stent for Small Vessels Work in Progress¹", Radiology, vol. 162, pp. 276-278, 1987. (PX 207).
- Letter from Palmaz to Bowman dated Mar. 17, 1986. (PX 350).
- Memo re: Minutes of Stent Project Review- San Antonio- Mar. 15, 1988. (PX 651).
- Kuntz, et al., Article: Clinical Cardiology Frontiers: "Defining Coronary Restenosis, Newer Clinical and Angiographic Paradigms", Circulation, Sep. 1993, vol. 88, No. 3, pp. 1310-1323. (PX 854).
- Belated Motion for Judgment with regard to Wolff Claims 1, 2-8, 10, 11, 13-17, and 19. (PX 1410).
- Drawing of Spiril Stent (sent to Bodic Mar. 17, 1986). (PX2933).
- Wright et al., Article: "Percutaneous Endovascular Stents: An Experimental Evaluation," Radiology, vol. 156, pp. 69-72, 1985. (PX 3093).
- Charnsangavej et al., Article: "A New Expandable Metallic Stent for Dilatation of Stenotic Tubular Structures: Experimental and Clinical Evaluation," Houston Medical Journal, vol. 3, pp. 41-51, Jun. 1987. (PX 3207).
- In re Application of Wiktor, Appln. No. 69,636, Response to Office Action dated Mar. 17, 1988. (PX3236).
- Transmittal Letter of Response to First Office Action in '417 patent. (PX 3993).
- Letter from B. Tobor to R. Schatz dated Jul. 23, 1991. (PX 3996).
- Mullins et al., Article: "Implantation of balloon-expandable intravascular grafts by catheterization in pulmonary arteries and systemic veins," Circulation, vol. 77, No. 1, pp. 188-189, 1988. (PX4049).
- Schatz et al., Article: "Intravascular Stents for Angioplasty," Cardio, 1997. (PX 4050).
- Schatz et al., Article: "New Technology in Angioplasty Balloon-Expandable Intravascular Stents, New Developments in Medicine," vol. 2, No. 2 pp. 59-75, 1987. (PX4051).
- Richard A. Schatz, Article: "Introduction to Intravascular Stents," Cardiology Clinics, vol. 6, No. 3, pp. 357-372, 1988. (PX 4052).
- Richard A. Schatz, Article: "A View of Vascular Stents," Circulation, vol. 79, No. 2, pp. 445-457, 1989. (PX4053).
- Wang et al., Article: "An Update on Coronary Stents," Cardio, pp. 177-186, 1992. (PX 4054).
- Richard A. Schatz, Article: "New Technology in Angioplasty: Balloon-Expandable Starts," Medicamundi, vol. 33, No. 3, pp. 112-116, 1988. (PX 4055).
- Letter from Tobor to Schatz dated Sep. 29, 1988. (PX 1395).
- Verified Statement of Facts by Unnamed Inventor R.A. Schatz document filed in U.S. Patent and Trademark Office on Sep. 8, 1989. (PX 3677).
- Declaration of John S. Kula Under 37 CFR § 1.672 (Exhibit 329).
- Letter to Mike Schular from R.A. Schatz dated Aug. 29, 1991. (Exhibit 402).
- Articulated, Balloon—Expandable Stents, (DBX 7159).
- J. Rosch et al., Experimental Intrahepatic Portacaval Anastomosis: Use of Expandable Gianturco Stents, Radiology, vol. 162, pp. 481-485, 1987.
- J. Rosch et al., Modified Gianturco Expandable Wire Stents In Experimental and Clinical Use, Ann Radiol, vol. 31, No. 2, pp. 100-103, 1987.
- J. Rosch et al., Gianturco Expandable Stents In the Treatment of Superior Vena Cava Syndrome Recurring After Vena Cava Syndrome Recurring After Maximum-Tolerance Radiation, Cancer, vol. 60, pp. 1243-1246, 1987.
- I.E. Gordon, Structures or Why Things Don't Fall Down, Penguin Books, pp. 45-59, 132-148, 210-244, 377-383.
- Maass et al., Radiological Follow-up of Transluminally Inserted Vascular Endoprostheses: An Experimental Study Using Expanding Spirals, Radiology, vol. 152, pp. 659-663, 1984.
- Argument submitted re EP 861 15473 dated Jan. 20, 1995. (AVE 2478).
- Verified Statement of Facts by Julio C. Palmaz dated Aug. 4, 1989. (PX 3662).
- Papanicolau et al., Insertion of a Biliary Endoprosthesis Using A Balloon Dilatation Catheter, Gastrointest Radiology, vol. 10, pp. 394-396, 1985.
- Palmaz et al., Atherosclerotic Rabbit Aortas: Expandable Intraluminal Grafting, Radiology, vol. 168, pp. 723-726, 1986.
- Palmaz, The Current Status of Vascular Prostheses; Rosch et al., Gianturco, Expandable Stents in Experimental and Clinical Use, SCITVR, pp. 118-124, 1987.
- Rosch et al., Abstract: Modified Gianturco Expandable Wire Stents in Experimental and Clinical Use, CIRSE, Porto Cervo, Sardinia, May 25-29, 1987.
- Rosch et al., Gianturco Expandable Wire Stents in the Treatment of Superior Vena Cava Syndrome Recurring After Maximum-Tolerance Radiation, Cancer, vol. 60, pp. 1243-1246, 1987.
- Mirich et al., Percutaneously Placed Endovascular Grafts for Aortic Aneurysms: Feasibility Study, Radiology, vol. 170, pp. 1033-1037, 1989.
- Dotter, Transluminally-placed Coilspring Endarterial Tube Grafts, Investigative Radiology, vol. 4, Sept.-Oct., pp. 329-332, 1969.
- Palmaz et al., Abstract: Expandable Intraluminal Graft: A Preliminary Study, Radiology, vol. 153 (P), Nov. 1983: 70th Scientific Assembly and Annual Meeting.
- Cragg et al., Nonsurgical Placement of Arterial Endoprostheses: A New Technique Using Nitinol Wire, Radiology, vol. 147, pp. 261-263, Apr. 1983.
- J. Rosch et al., Gianturco Expandable Stents in Experimental and Clinical Use, Program: "Twelfth Annual Course on Diagnostic Angiography and Interventional Radiology" (Society of Cardiovascular and Interventional Radiology, Pittsburgh, PA), Mar. 23-26, 1987 (the second Monofilament Article).
- Uchida et al., Modifications of Gianturco Expandable Wire Stents, AIR, vol. 150, pp. 1185-1187, 1988.
- Palmaz, Balloon-Expandable Intravascular Stent, AJR, vol. 1510, pp. 1263-1269.

US 7,300,662 B2

Page 10

Cordis Corporation v. Advanced Cardiovascular Systems, Inc., Guidant Corporation, Arterial Vascular Engineering, Inc., Boston Scientific Corporation and SCMED Life System, Inc., Plaintiffs Complaint, Oct. 23, 1997 (Case No. 97-550-SLR).

Arterial Vascular Engineering, Inc. v. Cordis Corporation, Johnson & Johnson and Expandable-Grafts Partnership, Plaintiffs First Amended Complaint for Declaratory Relief of Patent Validity, Unenforceability, Noninfringement, and for Antitrust Violations, Jan. 27, 1998 (Civil Action No. 97-700).

Arterial Vascular Engineering, Inc. v. Cordis Corporation, Johnson & Johnson and Expandable-Grafts Partnership, Cordis Corporation and Johnson & Johnson's Answer and Counterclaim, Feb. 27, 1998 (Civil Action No. 97-700-SLR).

Arterial Vascular Engineering, Inc. v. Cordis Corporation, Johnson & Johnson and Expandable-Grafts Partnership, Expandable-Graft Partnership's Answer, Feb. 27, 1998 (Civil Action No. 97-700-SLR).

Arterial Vascular Engineering, Inc. v. Cordis Corporation, Johnson & Johnson and Expandable-Grafts Partnership, Reply of Plaintiff Arterial Vascular Engineering, Inc. To Counterclaims of Defendant Cordis Corporation, Mar. 31, 1998 (Civil Action No. 97-700-SLR).

Arterial Vascular Engineering, Inc. v. Cordis Corporation, Johnson & Johnson and Expandable-Grafts Partnership, Reply of Plaintiff Arterial Vascular Engineering, Inc. To Counterclaims of Defendant Expandable Grafts Partnership, Mar. 31, 1998 (Civil Action No. 97-700-SLR).

Cordis Corporation v. Advanced Cardiovascular Systems, Inc. and Guidant Corporation Cordis Corporation's Motion for a Preliminary Injunction, Oct. 8, 1997 (Civil Action No. 97-550).

Cordis Corporation v. Advanced Cardiovascular Systems, Inc., Guidant Corporation Arterial Vascular Engineering, Inc., Boston Scientific Corporation and SCJVIED, Inc. Cordis's Motion for Preliminary Injunction Against Arterial Vascular Engineering, Inc., Dec. 29, 1997 (Case No. 97-550-SLR).

Deposition of R. Schatz, M.D. in *Cordis Corporation v. Advanced Cardiovascular Systems, Inc.*, taken on Jan. 8, 1998 (Civil Action No. 97-550 SLR).

Deposition of Lee P. Bendel in *Cordis Corporation v. Advanced Cardiovascular Systems, Inc.*, taken on Jan. 22, 1998 (Civil Action No. 97-550 SLR).

Deposition of Julio Cesar Palmaz in *Cordis Corporation v. Advanced Cardiovascular Systems, Inc.*, taken on Dec. 29, 1997 (Civil Action No. 97-550 SLR).

Deposition of Richard A. Bowman in *Cordis Corporation v. Advanced Cardiovascular Systems, Inc.*, taken on Jan. 9, 1998 (Civil Action No. 97-550 SLR).

Deposition of Gary Schneiderman in *Cordis Corporation v. Advanced Cardiovascular Systems, Inc.*, taken on Jan. 16, 1998 (Civil Action No. 97-550 SLR).

Deposition of David Pearle, M.D. in *Cordis Corporation v. Advanced Cardiovascular Systems, Inc.*, taken on Jul. 10, 1998 (Civil Action No. 97-550 SLR).

Preliminary Injunction hearing testimony taken on Feb. 9-13, 1998 (Civil Action No. 97-550 SLR).

Cordis Corporation v. Advanced Cardiovascular Systems, Inc., et al., (Civil Action No. 97-550 SLR) and *Cordis Corporation v. Advanced Cardiovascular Systems, Inc.* Et al. (Civil Action No. 98-65-SLR), Opening Post Hearing Brief of Plaintiff Cordis Corporation in Support of Motion for Preliminary Injunction, Mar. 6, 1998 (Portions relevant to patent claim construction and patent validity issues).

Cordis Corporation and Expandable Grafts Partnership v. Advanced Cardiovascular Systems, Inc. et al., Post-Hearing Reply Brief of Plaintiff Cordis Corporation in Support of Its Motion for Preliminary Injunction, Apr. 10, 1998 (Case No. 97-550 SLR) (Portions relevant to patent validity issues).

Cordis Corporation and Expandable Grafts Partnership v. Advanced Cardiovascular Systems, Inc., et al., Plaintiffs Motion for a Preliminary Injunction Against Boston Scientific Corporation and SCLMED Life Systems, Inc. And Memorandum in Support, Apr. 13, 1998 (Case No. 97-550-SLR).

Cordis Corporation and Expandable Grafts Partnership v. Advanced Cardiovascular Systems, Inc., et al., Judge Robinson's

Order Denying Plaintiffs Motion for a Preliminary Injunction, Jul. 17, 1998 (Civil Action No. 97-550 SLR).

Cordis Corporation and Expandable Grafts Partnership v. Advanced Cardiovascular Systems, Inc., et al., Defendant Boston Scientific Corporation and SCTMED Life Systems, Inc.'s Motion for Summary Judgment of Invalidity of U.S. Patent No. 5,102,417, Aug. 27, 1998 (Civil Action No. 97-550-SLR).

Boston Scientific Limited, et al. v. Expandable Grafts Partnership, Plaintiff's Statement of Claim, Mar. 13, 1997 (UK Action No. 1493).

Boston Scientific Limited, et al. v. Expandable Grafts Partnership, Defendant's Amended Defense and Counterclaim, Aug. 14, 1997 (UK Action No. 1493).

Boston Scientific Limited, et al. v. Expandable Grafts Partnership, Petition for Revocation, Mar. 13, 1997 (UK Action No. 1497).

Boston Scientific Limited, et al. v. Expandable Grafts Partnership, Particulars of Objections, Mar. 13, 1997 (UK Action No. 1497).

Boston Scientific Limited, et al. v. Expandable Grafts Partnership and Boston Scientific Limited et al., v. Julio C. Palmaz, Boston's Skeleton Argument (UK Action Nos. 1493, 1495, 1496, and 1497).

Boston Scientific Limited, et al. v. Julio C. Palmaz and Expandable Grafts Partnership, Skeleton Argument of Palmaz/EGP, Mar. 19, 1998 (UK Action Nos. 1493, 1495, 1496 and 1497).

Boston Scientific Limited, et al. v. Julio C. Palmaz and Expandable Grafts Partnership, EGP's Final Submissions, Apr. 2, 1998 (UK Action Nos. 1493, 1495, 1496 and 1497).

Boston Scientific Limited, et al. v. Julio C. Palmaz and Expandable Grafts Partnership, Judgment, Jun. 26, 1998 (UK Action Nos. 1493, 1495, 1496 and 1497).

Rosch, Modified Gianturco Expandable Wire Stents in Experimental and Clinical Use, CJR/SE 1987 Presentation: see Witness Statement of Josef Rosch from U.K. Proceeding.

Statement of Claim by Boston Scientific et al. against Expandable Grafts Partnership et al., in EGP et al. v. Boston Scientific et al. in Netherlands (Mar. 13, 1997).

Motion for Joinder of Actions, Change of Claim and Statement of Claim filed by Expandable Grafts Partnership et al. in EPG et al. v. Boston Scientific et al. In Netherlands (Apr. 22, 1997).

Opinion of K.J. Merman filed in EPG et al. v. Boston Scientific et al. in Netherlands (Aug. 29, 1997).

Expert report of Dr. Nigel Buller in EPG et al. v. Boston Scientific et al. in Netherlands (Aug. 28, 1997).

Expert report of Lee P. Bendel in EPG et al. v. Boston Scientific et al. in Netherlands (Aug. 28, 1997).

Memorandum or Oral Pleading in EPG et al. v. Boston Scientific et al. in Netherland (Sep. 12, 1997).

Plea Notes of P. A.M. in EPG et al. v. Boston Scientific et al. in Netherlands (Mar. 10, 1998).

Decision of Court of Appeals in EPG et al. v. Boston Scientific et al. In Netherlands (Apr. 23, 1998).

Translation of Nullity Action Against EPO 0 364 787 by Biotronik in Germany.

Translation of Nullity Action Against EPO 0 335 341 by Biotronik in Germany.

Translation of EPG Response to Nullity Action Against EP 0 364 787 by Biotronik in Germany.

Translation of EPG Response to Nullity Action EP 0 335 341 by Biotronik in Germany.

Nullity Suit Against EP-B1-0 335 341 Brought by Boston Scientific in Germany.

Translation of Opposition filed by Terumo Corp. Against Japan Patent No. 2680901.

Translation of Decision on Opposition Against Japan Patent No. 2680901.

Memorandum Order of the Court dated Sep. 7, 2000, concerning disputed claim construction.

Translation of Judgment in Nullity Action Against EP 0 364 787 by Biotronik in Germany.

Translation of Judgment in Nullity Action Against EP 0 335 341 by Biotronik in Germany.

Trial transcript from Mar. 17, 2005 at 171-172, 191-192.

Trial transcript from Mar. 18, 2005 at 282-285, 325-327, 349-351.

Trial transcript from Mar. 21, 2005 at 721-726.

US 7,300,662 B2

Page 11

Trial transcript from Mar. 24, 2005 at 1387.

Trial transcript from Jul. 26, 2005.

BSC's Opening Brief in Support of Its Motion for Judgment as a Matter of Law or, in the Alternative, for a New Trial, dated Mar. 16, 2001.

Cordis' Answering Brief in Opposition to BSC's Motion for JMOL or a New Trial on the Palmaz '762 Patent and the Schatz '332 Patents, dated Apr. 17, 2001.

BSC's Reply Brief in Support of Its Motion for Judgment as a Matter of Law or, in the Alternative, for a New Trial, dated May 11, 2001. J. Rosch et al., Abstract, Expandable Gianturco-Type Wire Stents in Experimental Intrahepatic Portacaval Shunts, Program: "72nd Scientific Assembly and Annual Meeting of the Radiological Society of North America", Nov. 30-Dec. 5, 1986, Radiology, vol. 161, pp. 40-41, 1986.

Cordis Corporation v. Boston Scientific, Order Dated Mar. 27, 2006 (97-550-SLR).

Cordis Corporation v. Boston Scientific, Judgment in a Civil Case Dated Mar. 27, 2006 (97-550-SLR).

Cordis Corporation v. Boston Scientific, Memorandum Opinion Dated Mar. 27, 2006 (97-550-SLR).

Cordis Corporation and Expandable Grafts Partnership v. Advanced Cardiovascular Systems, Inc., Guidant Corporation, Arterial Vascular Engineering, Inc., Boston Scientific Corporation and SCIMED Life Systems, Inc., Answer and Counterclaims of Defendant Advanced Cardiovascular Systems, Inc., Apr. 8, 1998 (Case No. 97-550-SLR).

Boston Scientific Limited et al. v. Expandable Grafts Partnership and Boston Scientific Limited et al. v. Julio C. Palmaz, Boston's Closing Submissions (UK Action Nos. 1493, 1495, 1496 and 1497).

Cordis Corporation v. Advanced Cardiovascular Systems, Inc., Guidant Corporation, Arterial Vascular Engineering, Inc., Boston Scientific Corporation and SCIMED Life Systems, Inc., Defendants' Answer, Nov. 12, 1997 (Case No. 97-550-SLR).

Statement of Rejoinder in the Action on the Merits, Also Including an Amendment of Defendant's Final Position in the Principal Action, as Well as the Provisional Statement of Rejoinder in the Action on the Counterclaim in *EPG et al. v. Boston Scientific et al.* In Netherlands (Feb. 10, 1998).

Statement of Answer in the Ancillary Appeal in *EPG et al. v. Boston Scientific et al.* in Netherlands (Mar. 10, 1998).

Appeal filed by Expandable Grafts Partnership et al. in *EPG et al. v. Boston Scientific et al.* in Netherlands (Nov. 12, 1997).

Title filed by Boston Scientific et al. in *EPG et al. v. Boston Scientific et al.* in Netherlands (Jan. 22, 1998).

Deposition of Richard Schatz, M.D. in *Cordis Corporation v. Advanced Cardiovascular Systems, Inc.* taken on Jul. 14, 1998 (Civil Action No. 97-550-SLR).

Jury Verdict form from the *Cordis Corporation et al v. Boston Scientific Corporation, et al* liability trial, undated.

Trial testimony transcripts from the *Cordis Corporation et al. v. Boston Scientific Corporation et al.* liability trial dated Nov. 27-Dec. 1, Dec. 4-8 and Dec. 11, 2000.

Boston Scientific SCIMED, Inc. and Boston Scientific Corporation v. Cordis Corporation and Johnson and Johnson, Inc., Opening Expert Report of Stephen R. Hanson, Ph.D. (Civil Action No. 03-283-SLR).

Boston Scientific SCIMED, Inc. and Boston Scientific Corporation v. Cordis Corporation and Johnson and Johnson, Inc., Opening Expert Report of Robson F. Storey, Ph.D. (Civil Action No. 03-283-SLR).

Boston Scientific SCIMED, Inc. and Boston Scientific Corporation v. Cordis Corporation and Johnson and Johnson, Inc., Rebuttal Expert Report of Kinam Park, Ph.D. (Civil Action No. 03-283-SLR).

Cordis Corporation v. Boston Scientific Corporation and SCIMED Life Systems, Inc. (C.A. No. 03-027-SLR) and *Boston Scientific SCIMED, Inc., and Boston Scientific Corporation v. Cordis Corporation and Johnson and Johnson, Inc.* (C.A. No. 03-283-SLR) Combined Post-Hearing Brief In Support Of Cordis Corporation's Motion For Preliminary Injunction in C.A. No. 03-027-SLR, And In Opposition to Plaintiffs' Motion For Preliminary Injunction in C.A. No. 03-283-SLR.

Cordis Corporation v. Boston Scientific Corporation and SCIMED Life Systems, Inc. (C.A. No. 03-027-SLR) *Boston Scientific SCIMED, Inc., and Boston Scientific Corporation v. Cordis Corporation and Johnson and Johnson, Inc.* (C.A. No. 03-283-SLR), Boston Scientific's Opening Post-Hearing Brief.

Cordis Corporation v. Boston Scientific Corporation and SCIMED Life Systems, Inc. (C.A. No. 03-027-SLR) *Boston Scientific SCIMED, Inc., and Boston Scientific Corporation v. Cordis Corporation and Johnson and Johnson, Inc.* (C.A. No. 03-283-SLR), Combined Post-Hearing Answering Brief In Support of Cordis Corporation's Motion For Preliminary Injunction In C.A. No. 03-027-SLR, And In Opposition To Plaintiffs Motion For Preliminary Injunction In C.A. No. 03-283-SLR.

Wu et al., Silicone-covered self-expanding metallic stents for the palliation of malignant esophageal obstruction and esophagorespiratory fistulas: experience in 32 patients and a review of the literature, *Gastrointestinal Endoscopy*, 1994, pp. 22-33, vol. 40, No. 1, Portland Oregon.

Binmoeller, et al., Silicone-Covered Expandable Metallic Stents in the Esophagus: An Experimental Study, *Endoscopy*, 1992, pp. 416-420, vol. 24, Georg Thieme Verlag Stuttgart New York.

Boston Scientific SCIMED, Inc., and Boston Scientific Corporation v. Cordis Corporation and Johnson and Johnson, Inc., Answering Memorandum in Opposition to Plaintiffs Motion for a Preliminary Injunction and Appendix thereto (Civil Action No. 03-283-SLR).

Boston Scientific SCIMED, Inc., and Boston Scientific Corporation v. Cordis Corporation and Johnson and Johnson, Inc., Plaintiff's Reply Brief in Support of Their Motion for Preliminary Injunction. Rhine, Polymers for Sustained Macromolecule Release: Procedures to Fabricate Reproducible Delivery Systems and Control Release Kinetics, *Journal of Pharmaceutical Sciences*, 1980, pp. 265-270, vol. 69, No. 3.

Langer et al., Controlled Release of Macromolecules From Polymers, *Biomedical Polymers Polymeric Materials and Pharmaceuticals for Biomedical Use*, 1980, pp. 112-137, Academic Press, Inc., New York, NY.

Langer et al., Applications of Polymeric Delivery Systems for Macromolecules and Factors Controlling Release Kinetics.

Rhine et al., A Method to Achieve Zero-Order Release Kinetics From Polymer Matric Drug Delivery Systems, pp. 67-72.

Langer et al., Polymers for the Sustained Release of Macromolecules: Controlled and Magnetically Modulated Systems, *Better Therapy With Existing Drugs: New Uses and Delivery Systems*; 1981, pp. 179-216, Merck Sharp & Dohme International, Rahway, NJ.

Hsieh, et al., Zero-Order Controlled-Release Polymer Matrices for Micro-and-Macromolecules, *Journal of Pharmaceutical Sciences*, 1983 pp. 17-22, vol. 72, No. 1.

Brown et al., In Vivo and In Vitro Release of Macromolecules from Polymeric Drug Delivery Systems, *Journal of Pharmaceutical Sciences*, 1983, pp. 1181-1185, vol. 72, No. 10.

Langer, Implantable Controlled Release Systems, *Pharmac. Ther.*, 1983, pp. 35-51, vol. 21, printed in Great Britain.

Kost et al., Controlled Release of Bioactive Agents, *Trends in Biotechnology*, 1984, pp. 47-51, vol. 2, No. 2, Elsevier BV Amsterdam.

Bawa et al., An Explanation for the Controlled Release of Macromolecules from Polymers, *Journal of Controlled Release*, 1985, pp. 259-267, vol. 1 Elsevier Science BV Amsterdam.

Leong et al., Polymeric controlled drug delivery, 1987, pp. 199-233, vol. 1/3, Elsevier Science Publishers BV Amsterdam.

Langer, Polymeric Delivery Systems, *Targeting of Drugs 2 Optimization Strategies*, 1989, pp. 165-174, Plenum Press, New York and London.

Langer, Biomaterials in Controlled Drug Delivery; New Perspectives from Biotechnological Advances; *Pharmaceutical Technology*, 1989, pp. 18, 23-24, 26, 28, 30.

Langer, Controlled Release Systems, pp. 115-124.

Laurencin et al., Polymeric Controlled Release Systems: New Methods for Drug Delivery, *Clinics in Laboratory Medicine*, 1987, pp. 301-323, vol. 7, No. 2, WB Saunders Company, Philadelphia.

Langer, Biopolymers in Controlled Release Systems, *Polymeric Biomaterials*, pp. 161-169.

US 7,300,662 B2

Page 12

- Tsong-Pin Hsu et al., Polymers for the Controlled Release of Macromolecules: Effect of Molecular Weight of Ethylene-vinyl Acetate Copolymer, *Journal of Biomedical Materials Research*, 1985, pp. 445-460, vol. 19.
- Langer, Polymers and Drug Delivery Systems, *Long-Acting Contraceptive Delivery Systems*, 1983, pp. 23-32, Harper & Row, Philadelphia, PA.
- Langer, New Drug Delivery Systems: What the Clinician Can Expect, *Drug Therapy*, 1983, pp. 217-231.
- Langer, et al., Chemical and Physical Structure of Polymers as Carriers for Controlled Release of Bioactive Agents: A Review, *Rev Macromol. Chem. Phys.*, 1983, pp. 61-126.
- Langer, Polymeric Delivery Systems for Controlled Drug Release, *Chem. Eng. Commun.* 1980, pp. 1-48-vol. 6, Gordon and Breach Science Publishers, Inc. USA.
- Langer, et al., Biocompatibility of Polymeric Delivery Systems for Macromolecules, *Journal of Biomedical Materials Research*, 1981, pp. 267-277, vol. 15.
- Langer, Controlled Release: A New Approach to Drug Delivery, *Technology Review*, 1981, pp. 26-34.
- Langer, et al Sustained Release of Macromolecules from Polymers, *Polymeric Delivery Systems*, PGS. 175-176, Gordon and Breach Science Publishers, New York.
- Langer, Polymers for the Sustained Release of Proteins and other Macromolecules, *Nature*, 1976, pp. 797, 263, 799-800, vol. 263, No. 5580.
- Baker, et al., Controlled Release: Mechanisms and Rates (1974).
- Hanson, et al., In Vivo Evaluation of Artificial Surfaces with a Nonhuman Primate Model of Arterial Thrombosis, *Lab Clin. Med.*, Feb. 1980, pp. 289-304.
- Baker, Controlled Release of Biologically Active Agents (1987) pp. 1-275.
- Cordis Corporation v. Boston Scientific Corporation* (CA. No. 03-27-SLR) and *Boston Scientific Scimed, Inc., v. Cordis Corporation and Johnson & Johnson, Incorporated* (CA. No. 03-283-SLR) Hearing Transcripts for Jul. 21, 2003, Jul. 22, 2003, Jul. 23, 2003.
- Cordis Corporation v. Boston Scientific Corporational* et al. (CA. No. 03-027-SLR), and *Boston Scientific Scimed, Inc. et al. v. Cordis Corporation* et al. (CA. No. 03-283-SLR), Boston Scientific's Post-Hearing Reply Brief and Exhibits Thereto, Sep. 12, 2003.
- Cordis Corporation v. Boston Scientific Corporation* et al. (CA. No. 03-027-SLR), and *Boston Scientific Scimed, Inc. et al. v. Cordis Corporation* et al. (CA. 03-283-SLR), Memorandum Order, Nov. 21, 2003.
- Cordis Corporation v. Boston Scientific Corporation* et al. (CA. No. 03-027-SLR), and *Boston Scientific Scimed, Inc. et al. v. Cordis Corporation* et al (CA. No. 03-283-SLR), Deposition Transcript of Julio C. Palma.
- Arterial Vascular Engineering, Inc. v. Cordis Corporation, Johnson & Johnson and Expandable Grafts Partnership*, Cordis Corporation and Johnson & Johnson's Answer and Counterclaim, Feb. 27, 1998 (Civil Action No. 97-700-SLR).
- Plea Notes in *EPG et al. v. Boston Scientific* et al. in Netherlands (Sep. 12, 1997).
- Provisional Judgment *EPG et al. v. Boston Scientific* et al. in Netherlands (Oct. 29, 1997).
- Trial testimony transcripts from the Cordis Corporation et al. v. Medtronic AVE Inc., et al. liability trial dated Nov. 6-9, 13-17 and 20-21, 2000.
- Jury verdict form from the *Cordis Corporation et al. v. Medtronic AVE, Inc. et al.* liability trial.
- Hearing testimony transcript from the consolidated *Cordis Corporation et al. v. Medtronic AVE, Inc. et al. and Boston Scientific Corporation et al.* inequitable conduct hearing dated Feb. 7-9 and 12, 2001.
- Cordis Corporation v. Medtronic Ave., Inc. et al.*, OPINION, 97-550-SLR, dated Mar. 28, 2002.
- Cordis Corporation v. Advanced Cardiovascular Systems, Inc. et al.* (CA. No. 97-550-SLR), *Medtronic AVE, Inc. v. Cordis Corporation et al.* (CA. No. 97-700-SLR), *Boston Scientific Corporation v. Athicon, Inc. et al.* (CA. No. 98-19-SLR), Expert Report of John T. Gookasian, Esq.
- Cordis Corporation v. Advanced Cardiovascular Systems, Incet al.* (CA. No. 97-550-SLR), *Medtronic A VE, Inc. v. Cordis Corporation et al* (CA. No. 97-700-SLR), *Boston Scientific Corporation v. Athicon, Inc. et al* (CA. 98-19-SLR), Expert Report of John F. Witherspoon.
- Ruef, Johannes MD, et al.; "Flavopiridol Inhibits Smooth Muscle Cell Proliferation In Vitro and Neointimal Formation In Vivo After Carotid Injury In The Rat"; From the Division of Cardiology and Sealy Center for Molecular Cardiology, University of Texas Medical Branch, Galveston; Accepted Apr. 9, 1999; Circulation Aug. 10, 1999; pp. 659-665.
- European Search Report EP 05 25 2466 dated Jul. 26, 2005.
- European Search Report EP 05 25 2631 dated Jul. 26, 2005.
- European Search Report EP 05 25 2478 dated Jul. 26, 2005.
- Schuler, W. et al., "SDZ RAD, A New Rapamycin Derivative: Pharmacological Properties In Vitro and In Vivo," *Transplantation*, Jul. 5, 1997, 64(1), 36-42.

* cited by examiner